Comparison of Brain Structure and Function Between Adolescents with Autism Spectrum Disorder and Adolescents with Obsessive- Compulsive Disorder

Carlisi, Christina Owen

Awarding institution:
King's College London

Comparison of Brain Structure and Function Between Adolescents with Autism Spectrum Disorder and Adolescents with Obsessive-Compulsive Disorder

---

Christina Owen Carlisi

Institute of Psychiatry, Psychology and Neuroscience

Thesis Submitted to King's College London for the Degree of Doctor of Philosophy

Supervisors: Professor Katya Rubia and Professor Declan Murphy

Examiners: Professor Naomi Fineberg and Professor Bhismadev Chakrabarti

2017

ABSTRACT

Autism Spectrum Disorder (ASD) and Obsessive-Compulsive Disorder (OCD) are frequently comorbid and share deficits in executive function, highlighting a need to understand the shared and/or disorder-specific neurofunctional abnormalities underlying these behaviours.

First, a comparative, multimodal meta-analysis between ASD and OCD was conducted on whole-brain voxel-based morphometry structural magnetic resonance imaging (MRI) studies and functional MRI studies of cognitive control. Second, functional MRI (fMRI) was used to scan adolescent boys with ASD or OCD, and control boys while they performed tasks measuring sustained attention and reward-based decision-making, including temporal discounting and gambling.

Shared abnormalities were observed in the meta-analysis, where both clinical groups had reduced structure and function during cognitive control in medial prefrontal and anterior cingulate regions. During fMRI, shared abnormalities were also observed during executive function tasks of reward-based decision-making, where both clinical groups had reduced activation in ventromedial, inferior frontal and orbitofronto-striatal as well as temporo-parietal regions compared to controls.

Disorder-specific abnormalities, on the other hand, were seen predominantly during tasks of non-emotional executive function. OCD patients had disorder-specific increases in striato-insular structure and function, whereas ASD individuals had increased structure but decreased function in dorsolateral prefrontal cortex during cognitive control. Temporo-parietal underactivation during sustained attention was uniquely associated with OCD compared to ASD and controls.

These results present novel evidence that neurofunctional abnormalities, including temporo-parietal underactivation and striato-insular overactivation during non-emotional tasks of executive function may be mostly disorder-specific to OCD compared with ASD, whereas abnormalities during emotionally-driven tasks of reward-based decision-making are predominantly shared between ASD and OCD, particularly in ventromedial, inferior and orbitofronto-striatal regions. These studies provide preliminary indication that both shared and disorder-specific neurostructural and neurofunctional biomarkers underpin cognitive dysfunction in these disorders that may have implications for future diagnosis and treatment.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

ADI-R: Autism Diagnostic Interview – Revised

ADOS: Autism Diagnostic Observation Schedule

ASD: Autism Spectrum Disorders

CY-BOCS: Children's Yale-Brown Obsessive Compulsive Scale

DSM: *Diagnostic and Statistical Manual of Mental Disorders*

OCD: Obsessive-Compulsive Disorder

RRBIs: Restricted, repetitive and stereotyped behaviours and interests

SCQ: Social Communication Questionnaire

SDQ: Strengths and Difficulties Questionnaire

SSRI: selective serotonin reuptake inhibitor

Y-BOCS: Yale-Brown Obsessive Compulsive Scale

CPT: continuous performance test

EF: Executive function

IGT: Iowa Gambling task

SAT: sustained attention task

TD: temporal discounting

ToM: Theory of Mind

WCST: Wisconsin Card Sort task

WM: working memory

ANOVA: analysis of variance

ANCOVA: analysis of covariance

BOLD: Blood-Oxygen Level-Dependent

CT: Computerised Tomography

DTI: diffusion tensor imaging

EEG: electroencephalography

fMRI: functional magnetic resonance imaging

FWHM: full-width at half-maximum

GMV: grey matter volume

MRI: magnetic resonance imaging

PET: Positron Emission Tomography

ROI: region of interest

sMRI: structural magnetic resonance imaging

SPECT: Single-Photon Emission Computed Tomography

TBV: total brain volume

ACC: anterior cingulate cortex

BG: basal ganglia

CTSC: cortico-striato-thalamo-cortical

dACC: dorsal anterior cingulate cortex

DLPFC: dorsolateral prefrontal cortex

dmPFC: dorsomedial prefrontal cortex

FEF: frontal eye field

IFC: inferior frontal cortex

IFG: inferior frontal gyrus

IPL: inferior parietal lobe

IPS: intraparietal sulcus

MFG: middle frontal gyrus

mPFC: medial prefrontal cortex

MTL: middle temporal lobe

NAcc: nucleus accumbens

OFC: orbitofrontal cortex

PCC: posterior cingulate cortex

PFC: prefrontal cortex

rACC: rostral anterior cingulate cortex

rMPFC: rostromedial prefrontal cortex

STL: superior temporal lobe

TPJ: temporo-parietal junction

VLPFC: ventrolateral prefrontal cortex

vmOFC: ventromedial orbitofrontal cortex

vmPFC: ventromedial prefrontal cortex

VS: ventral striatum

ACKNOWLEDGEMENTS

There are a number of individuals to whom I owe much gratitude.

I would first and foremost like to thank the families and individuals who took part in these studies. Aside from their participation, these boys afforded an invaluable spirit of curiosity and enthusiasm to my research. I would also like to thank the National Institute for Health Research Biomedical Research Centre for funding my PhD and the Medical Research Council for funding these studies.

There are a number of mentors and colleagues without whom this research would not have been possible. To my primary supervisor Professor Katya Rubia, her teaching and belief in me as a young scientist has fundamentally empowered me with the tools to continue in an academic research career; I have learned an immeasurable amount under her supervision. I must also thank Professor Declan Murphy and Professor David Mataix-Cols for their insightful advice, comments and conversation, and Dr Vincent Giampietro for his kindness, patience and continual willingness to help. And to Dr Kaylita Chantiluke, Dr Clodagh Murphy, and Dr Anastasia Christakou, for their valued advice and huge help with data collection. To Dr Bruce Clark and the entire OCD team at the Michael Rutter Centre, your support made this work not only possible, but more importantly, truly enjoyable and an instrumental clinical learning experience. Special mention goes to Ella Duvall, who quietly suffered my endless emails and went above and beyond to help with recruitment.

To friends and colleagues – Analucia Alegria Alzamora (and her record-time proofreading), Luke Norman, Dr Helen Brinson and Dr Melanie Wulff (and her MS Word wizardry), days in the office would not have been the same without your conversation, advice, and empathetic ears. It has truly been a pleasure to work with you all. And to my little yoga community, especially to Harriet Bone, your peace and insight has kept me focused, present and (quite literally) breathing during this process.

To all the friends I've met at the IoPPN, your endless support and friendship has made this experience truly gratifying and one that will last long after the PhD; Dr Ottilie Sedgwick and Dr Clementine Edwards, your love, laughter and reassurance have provided emotional respite when it was most needed…and if there's one thing I'm proudest of, it's finally knowing the difference between a purse and a wallet. And to all other dear friends and Lunch Club members, Dave (your always frank advice never

ceases to be refreshing), Karlijn, Viktoria, Ben (and his hats), Paolo and everyone else, your friendship and humour have made even the toughest days more bearable. A special thanks to Toby Wise, with whom many negronis and conference discos have been shared. Your knowledge and love for teaching (and Python) is an inspiration, and your willingness to take on any challenge big or small has literally gotten me through this PhD (undoubtedly a lot faster than I would have done otherwise).

I'd also like to thank all dogs everywhere. They never fail to lift my spirits and have inspired my new career path in the field of dog MRI research. Only kidding. Kind of.

To my parents, for their endless support, encouragement and love, despite the distance and despite the fact that I'm pretty sure they still don't know what I've spent the last 3 years doing.

And finally to Oli, for your inspiration, love, and most of all patience. You have put up with me. You have taught me. You keep me going. I owe so much to your guidance, and I simply could not have done this without you.

CHAPTER 1 - NEUROPSYCHOLOGICAL EVIDENCE OF EXECUTIVE DYSFUNCTION IN ASD AND OCD

1.1 Introduction

According to the Diagnostic and Statistical Manual of Mental Disorders-V (DSM-V; http://www.dsm5.org/ (American Psychiatric Association, 2013)), Autism Spectrum Disorder (ASD) is an encompassing term for a group of neurodevelopmental disorders characterised by a 'triad' of impairments in social interaction and communication as well as restricted, repetitive and stereotyped behaviours and interests (RRBIs), as described initially by Wing and Gould (Wing and Gould, 1979). To receive a diagnosis of ASD, an individual must exhibit all three of these symptom components (although the 5th edition of the DSM (American Psychiatric Association, 2013) collapses communication and social difficulties into one category). ASD symptoms usually emerge between 3-5 years of age when communication and social relationships become important for typical development, but symptoms can be present and detected as early as the first year of life. Clinical diagnosis of ASD is most commonly made using one of two widely used diagnostic interviews: the Autism Diagnostic Interview – Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS). The ADI-R is a detailed interview with the primary carer of an individual and assesses symptoms related to the triad and their past and current prevalence (Lord et al., 1994). The ADOS is a series of tasks that vary based on the verbal abilities of an individual and which are conducted with the individual to assess the presence of autistic traits based on the triad of symptoms (Lord et al., 2000). Prevalence estimates of ASD across the lifespan range from 0.6-1% (Baird et al., 2006), and the disorder commonly persists into adulthood, with overall estimates around 1%, but closer to 2% in men and 0.2% in women (Brugha et al., 2011).

ASD has a higher prevalence in males compared to females, with average estimates of about 4:1 (Rivet and Matson, 2011). However, these ratios are closer to 10:1 in high functioning autism but fall to 2:1 in more severe cases that often include intellectual disability (Fombonne, 2009). Early theories proposed by Baron-Cohen et al. suggest that this high male prevalence may be due to an "extreme male brain" (Baron-Cohen and Hammer, 1997), related to varied factors including foetal testosterone levels (Baron-Cohen et al., 2011). However, other recent work suggests that it may be at least partially due to a female "protective effect" (Skuse, 2000), such that girls require a greater aetiological load to manifest ASD-related symptoms (Robinson et al., 2013). Alternatively, a female "masking effect" (Kopp and Gillberg, 1992) has been proposed, where girls' increased social interests and more socially 'normal' RRBIs mask symptoms of ASD (Van Wijngaarden-Cremers et al., 2014). Nonetheless, there is clinical under-representation and under-diagnosis in females with ASD, particularly in cases where intellectual disability is relatively unaffected (Dworzynski et al., 2012). Moreover, ASD is a highly heterogeneous condition and carries rates of comorbidity with a number of other psychiatric disorders, including ADHD and anxiety, that have been estimated as high as 30-40% (Leyfer et al., 2006) since the allowance of co-diagnosis of other disorders with ASD in DSM-V (American Psychiatric Association, 2013).

Another disorder that commonly presents in childhood is obsessive-compulsive disorder (OCD). DSM-V defines OCD as a disorder characterised by recurring, intrusive and distressing thoughts, known as obsessions, and ritualistic, repetitive behaviours, known as compulsions (American Psychiatric Association, 2013). In clinical settings, compulsions are commonly seen as goal-driven behaviours that a patient performs in response to an obsession, anxiety or threat he or she is trying to ignore or suppress (Robbins et al., 2012). This has been termed a 'cognitive' account of

OCD in the neuropsychological literature, suggesting problems with outcome valuation (Salkovskis et al., 2000), but other theories have been proposed suggesting that OCD arises from goal-directed dysfunction that interacts with an inability to exert control over response to anxiety, meaning that compulsions do not necessarily arise as a consequence of obsessions (Gillan and Robbins, 2014).

While OCD is a highly heterogeneous disorder, symptoms have been divided into 4 broad categories, (1) responsibility obsessions and checking rituals, (2) contamination obsessions and decontamination/washing rituals, (3) symmetry obsessions and ordering/arranging and counting rituals and (4) aggressive, sexual, somatic and religious obsessions and mental and reassurance seeking rituals (Mataix-Cols et al., 2005, Abramowitz et al., 2010). Clinical symptoms of OCD are most commonly indexed using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al., 1989) symptom checklist, or the Children's Y-BOCS (CY-BOCS) in paediatric populations (Scahill et al., 1997). The Y-BOCS is a detailed rating scale of OCD symptom severity split into obsessions and compulsions including items assessing how much time is taken and distress is caused by each symptom. OCD prevalence estimates range between 1-3% worldwide (Ruscio et al., 2010), with an overall average age of onset around 19.5 years, although one-half to one-third of individuals experience onset in childhood/adolescence, with one in five individuals experiencing onset before age 10 (Ruscio et al., 2010). A bimodal distribution of age of onset has been described, with mean age of early onset around 11 years and mean age of late onset around 23 years (Taylor, 2011), with a higher proportion of males with early onset but a slightly higher proportion of females with late onset OCD (Fontenelle et al., 2006, Mathis et al., 2011), as reported by clinic-based studies. However, epidemiological surveys of adolescents report equivalent gender ratios, or even a slightly higher prevalence in females (Shafran, 2001). It has also been shown that individuals with childhood-onset

OCD are more likely to have a family member with OCD, suggesting a possible genetic link in the aetiology of early-onset subtypes of the disorder (Piacentini and Bergman, 2000).

At an observational level, ASD and OCD can share certain behavioural characteristics; repetitive behaviours are among the core symptom features of both disorders (Anholt et al., 2010), and impulsive and compulsive behaviours have been cited as important characteristics of both disorders (Fineberg et al., 2009). Both disorders are also highly heterogeneous (Rasmussen and Eisen, 1992, Wiggins et al., 2012) and can be clinically difficult to separate (Doshi-Velez et al., 2014). Rates of comorbidity of OCD in children with ASD have been estimated to be as high as 37% (Leyfer et al., 2006), while rates of comorbid ASD in individuals with OCD have been more conservatively estimated at around 6% (Murray et al., 2015), possibly due to the fact that the co-diagnosis of any disorder with ASD was only recently allowed in the latest edition of the DSM (DSM-V; (American Psychiatric Association, 2013)). Repetitive rituals in ASD are sometimes conflated with compulsive behaviours in OCD, and compulsive behaviour is a core symptom domain of autism (Fineberg et al., 2009, Hollander et al., 2016). One study (Hollander et al., 2003) investigated rate of RRBIs in children with ASD (as indexed by the ADI-R) and the relationship of these rates with obsessive-compulsive traits (as indexed by the Y-BOCS) in parents of children with ASD and found that children with higher rates of RRBIs were more likely to have at least one parent with obsessive-compulsive traits or OCD, demonstrating that the aetiological overlap of repetitive behaviours may at least partially be familial/genetic (although larger twin studies are needed to further confirm this theory).

However, theories conceptualizing repetitive behaviours in each disorder associate repetitive rituals in ASD with reward-seeking and self-pacifying behaviour,

whereas compulsions in OCD are more commonly associated with harm avoidance and anxiety-mediating behaviour (Menzies et al., 2007, Fineberg et al., 2009, Fineberg et al., 2014). Despite this dichotomy, more recent theories of a 'compulsivity-impulsivity spectrum' (Hollander et al., 2016) suggest that while aspects of these two behaviours are driven to some degree by distinct cortico-subcortical circuitry, there is increasing evidence to suggest that compulsivity and impulsivity share neuropsychological mechanisms of 'dysfunctional inhibition of thoughts and behaviours' (Hollander et al., 2016), indicated by cognitive inflexibility related to attentional bias, motor disinhibition, and disadvantageous decision-making. Researchers have identified common symptoms of behavioural disinhibition in both ASD and OCD that may sustain repetitive rituals and compulsive behaviour in each disorder (Fineberg et al., 2009). Some studies have even identified obsessive-compulsive behaviours as a behavioural phenotype of ASD (Jacob et al., 2009), with studies in children reporting increased obsessive-compulsive symptoms in children with ASD relative to those without (Russell et al., 2005, Leyfer et al., 2006), as well as increased frequency of ASD symptoms in children with OCD (Ivarsson and Melin, 2008). Another study found that paediatric patients with mood and anxiety disorders reported higher scores on ASD symptom scales compared to typically developing children and children with non-OCD related anxiety disorders (Pine et al., 2008). Efforts have been made to amend current OCD rating scales to account for ASD symptoms (Scahill et al., 2006), but such attempts have provided limited utility in relation to more widely validated ASD measures of repetitive behaviours. Despite this evidence of behavioural overlap between ASD and OCD, relatively little is known about shared and disorder-specific neurobiological abnormalities that might mediate traits and symptoms seen in each disorder. An improved understanding of such shared and disorder-specific mechanisms

including neurofunctional activity and brain structure is key to the development of new diagnostic tools as well as the potential identification of treatment targets.

However, before such biomarkers can be addressed, it is critical to focus on neuropsychological processes and deficits, as these mechanisms underpin the cognitive impairments that are often observed in both ASD and OCD and which are hypothetically mediated by associated abnormalities in brain-based mechanisms driving such impairments. A subset of neuropsychological deficits includes impairments in executive function (EF). EF is defined as a set of higher-level cognitive functions important for deliberate, motivated behaviours including the formation, planning, execution and modification of goal-directed actions (Zelazo et al., 2004). Cognitive domains of EF include planning, working memory, temporal foresight, set-shifting, inhibition and motivated decision-making (Zelazo et al., 2004, Stuss and Alexander, 2007, Rubia, 2011). While attention functions are less commonly included in more traditional definitions of EF, higher-level and selective attention are indeed important for goal-directed behaviour and will be discussed in this thesis within the context of EF (Zelazo et al., 2004). EFs can be distinguished into two domains: "cool" EF refers to non-emotional abstract functions such as selective and sustained attention and inhibition, and is mediated by ventrolateral and dorsolateral fronto-striatal, fronto-cerebellar and fronto-parietal brain networks (Zelazo and Müller, 2007). "Hot" EF refers to emotionally-valenced reward-related decision-making or motivation control measured in tasks of e.g. gambling, temporal discounting and reward-based learning and is mediated by mesolimbic ventromedial prefrontal (VMPFC) and orbitofrontal (OFC)-striatal and limbic circuitry (Zelazo and Müller, 2007). The terms "cool" and "hot" EF are used throughout this thesis to differentiate between tasks involving low vs. high levels of affective/motivational processing (Hybel et al., 2016), although it should be noted that the validity and utility of this distinction has been debated in recent years

in the context of child neuropsychology (Welsh and Peterson, 2014). Nonetheless, both domains of EF change and develop across adolescence (Kerr and Zelazo, 2004, Christakou et al., 2011). Neurocognitive performance deficits across a range of EF tasks have been observed in both ASD (Hill, 2004, Kenworthy et al., 2009, Brunsdon et al., 2015, Lai et al., 2016) and OCD (Cavedini et al., 2010, Abramovitch et al., 2013, Brem et al., 2014, Abramovitch et al., 2015a), and as such, ASD and OCD have been suggested to be disorders of executive dysfunction (Pennington and Ozonoff, 1996, Ozonoff, 1997, Russell, 1997, Lai et al., 2016). Moreover, both domain-general accounts (Hill, 2004) and triadic models (Brunsdon et al., 2015) of ASD have linked EF problems specifically to RRBIs. Hill and colleagues have suggested that while two prominent theories of ASD, the social motivation hypothesis and the weak central coherence theory, may explain many of the symptoms related to the overall ASD phenotype, RRBIs may be best explained by executive dysfunction. This association has been made in cool EF domains such as cognitive flexibility, particularly in contexts where explicit rules are not present, as well as planning (Hill, 2004), and such deficits have been distinguished from other disorders such as ADHD, which show more consistent deficits in inhibitory control functions but less so in planning, suggesting a possible and specific link to RRBIs commonly observed in ASD (Pennington and Ozonoff, 1996). Similar links between repetitive compulsive behaviours and EF deficits have been made in OCD. For example, some have hypothesised that checking compulsions may result from working memory deficits (Woods et al., 2002). Other studies have suggested that impaired response inhibition in OCD may be an endophenotypic marker of clinically observed compulsive behaviours (Chamberlain et al., 2005). Thus, identifying EF profiles of ASD and OCD could establish which cognitive functions would be beneficial to investigate at a neurofunctional level and elucidate symptom overlap and specificity between these disorders. Based on the scope

of this PhD thesis, investigations of EF domains including 1) cognitive control, 2) sustained attention, 3) temporal foresight and related functions, and 4) gambling and reward learning will be discussed in detail. Other EF deficits that are relevant to each disorder and implicated in the four domains mentioned above but do not specifically pertain to this thesis will be reviewed briefly.

1.2 Cognitive control and inhibition

1.2.1 Cognitive control in ASD

Cognitive control is typically measured with tasks of motor and interference inhibition but can also include the domains of task-switching and cognitive flexibility (Miyake et al., 2000, Miller and Cohen, 2001, Aron, 2011). Motor response inhibition refers to selective inhibition or the withdrawal of a built up pre-potent response to frequent stimuli after the presentation of an infrequent 'no-go' or 'stop' signal, thus giving rise to Go/No-Go and Stop Signal paradigms (Rubia et al., 2007). Interference inhibition is typically measured with Stroop, Simon or Erikson Flanker tasks and requires the ability to inhibit a pre-potent response tendency that conflicts with the primary intended action. Switching requires an ability to inhibit previously valid stimulus-response associations and engage in new associations when task rules or conditions change (Rubia et al., 2007). Although there are slight differences among these tasks of cognitive control, recent evidence points towards shared inhibitory processes across these domains that are mediated by overlapping brain networks (Hugdahl et al., 2015).

Work investigating motor response and interference inhibition deficits in ASD has suggested that inhibitory control is interdependent with other EFs impaired in children with ASD such as working memory (WM) (Solomon et al., 2008). Moreover,

evidence suggests a link between RRBIs and cognitive control abnormalities in ASD (Lopez et al., 2005, Langen et al., 2011), as well as the implication of cognitive control in attention functions also impaired in ASD (Rubia et al., 2010a). Evidence consistently points to poor performance among children and adolescents with ASD on motor response inhibition paradigms including Stop Signal (Verte et al., 2005, Lemon et al., 2011, de Vries and Geurts, 2014) and Go/No-Go tasks (Bishop and Norbury, 2005, Christ et al., 2007), and this evidence is further supported by reviews of deficits in pre-potent response inhibition in ASD (Hill, 2004, O'Hearn et al., 2008, Sanders et al., 2008). On the other hand, evidence supports relatively intact interference inhibition on Stroop tasks (Ozonoff and Jensen, 1999, Russell et al., 1999, Christ et al., 2007, Adams and Jarrold, 2009, Christ et al., 2011) although there have also been findings of impaired performance in paediatric ASD populations on Stroop (Verte et al., 2005, Robinson et al., 2009, Vaidya et al., 2011) and related interference inhibition tasks (Solomon et al., 2014). Such discrepancies are possibly due to the heterogeneous nature of ASD as well as different paradigms and small sample sizes.

In line with the prominence of restricted and repetitive behaviours and resistance to change in ASD, cognitive inflexibility has been examined as a possible underlying mechanism of this phenotype. Studies employing the Wisconsin Card Sorting Test (Ozonoff et al., 1991, Ozonoff and McEvoy, 1994, Ozonoff, 1995, Bennetto et al., 1996, Verte et al., 2005, Van Eylen et al., 2011, Landry and Al-Taie, 2016, Westwood et al., 2016, Yeung et al., 2016), set-shifting (Hughes et al., 1994, Ozonoff et al., 2000, Yerys et al., 2009), switching (Yerys et al., 2011) and reversal learning (McEvoy et al., 1993, Coldren and Halloran, 2003, Yerys et al., 2007, Loveland et al., 2008, Zalla et al., 2009) have shown impairments in cognitive flexibility in ASD children relative to controls, and this impairment correlates with severity of repetitive behaviours (Yerys et al., 2009). However, some studies, especially those investigating very young patients

(Dawson et al., 2002, Lionello-DeNolf et al., 2008), have shown no behavioural impairments in this domain (Geurts et al., 2009, Chantiluke et al., 2015a).

1.2.2 Cognitive control in OCD

OCD has traditionally been conceptualised as a disorder of compulsivity (Voon et al., 2015), but evidence suggests that impulsivity is an important intermediate phenotype implicated in the disorder, associated with poor top-down inhibitory control resulting in a failure to inhibit certain behaviours (Fineberg et al., 2009, van Velzen et al., 2014). Moreover, cognitive flexibility requires flexible attention and executive control of attention in addition to cognitive control (Yeung et al., 2006). Thus, this domain may be especially important in OCD, as an inability to shift attention may contribute to the persistence of internal thought patterns (Graybiel, 2000). Therefore, one would expect that individuals with OCD might exhibit neurocognitive deficits in cognitive and inhibitory control. Cognitive control impairments have been found in adolescents with OCD during task-switching (Britton et al., 2010), but another study in adolescents with OCD found no inhibition impairments in patients relative to controls during motor response inhibition (Hybel et al., 2016). A number of studies in adults have found impairments in motor response inhibition (Chamberlain et al., 2006, Penadés et al., 2007, Boisseau et al., 2012, Kang et al., 2013, Morein-Zamir et al., 2014, Sohn et al., 2014) and interference inhibition (Bannon et al., 2002, Nabeyama et al., 2008, Nakao et al., 2009b, Schlösser et al., 2010), although a more recent study of multiple tasks investigating inhibitory control in adults with OCD found no performance deficits on any of the tasks (Morein-Zamir et al., 2015). It should be noted, however, that many of these tasks were completed as part of functional magnetic resonance imaging (fMRI) studies, and fMRI task versions often lose behavioural sensitivity in favour of more sensitive measures of brain activation. Overall, results

support deficits in varied domains of inhibitory control, albeit primarily in studies of adults with OCD, but conflicting findings and unimpaired performance may be due to sample heterogeneity, age, and medication/treatment status often seen in studies of OCD.

1.2.3 Summary of cognitive control in ASD and OCD

Collectively, this evidence suggests cognitive control deficits across motor and interference inhibition as well as switching in both ASD and OCD. Both disorders have shown behavioural impairments across motor response inhibition tasks (Hill, 2004, Bishop and Norbury, 2005, Verte et al., 2005, Chamberlain et al., 2006, Christ et al., 2007, Penadés et al., 2007, O'Hearn et al., 2008, Sanders et al., 2008, Lemon et al., 2011, Boisseau et al., 2012, Kang et al., 2013, de Vries and Geurts, 2014, Morein-Zamir et al., 2014, Sohn et al., 2014), while interference inhibition seems to be relatively less affected in individuals with ASD (Ozonoff and Jensen, 1999, Russell et al., 1999, Christ et al., 2007, Adams and Jarrold, 2009, Christ et al., 2011) (although some studies have found interference inhibition deficits in ASD, especially on the Stroop task (Verte et al., 2005, Robinson et al., 2009, Vaidya et al., 2011). Moreover, the majority of studies in OCD have been conducted in adult samples, so the developmental or age-related effects of observed deficits remain relatively unexplored. Nonetheless, cognitive control is an important construct to investigate in both ASD and OCD; cognitive impairments on these tasks have been linked to clinical symptoms of repetitive behaviours in ASD (Lopez et al., 2005, Yerys et al., 2009, Langen et al., 2011), and although similar hypotheses of associations between task performance and OCD-related symptoms have not been proposed or tested, evidence suggests that OCD symptoms may result from impaired top-down inhibitory control, presumably resulting in a failure to inhibit certain compulsive behaviours (Fineberg et al., 2009, van Velzen et al., 2014). Thus, additional

investigation of cognitive control abnormalities in these disorders is warranted. Furthermore, understanding the neural underpinnings of these abnormalities may elucidate the degree to which these deficits are shared or disorder-specific and how they may possibly relate to clinical symptoms. A comparative review and meta-analysis of fMRI studies investigating brain function in ASD and OCD during cognitive control is presented in Chapter 4.

1.3 Attention functions

1.3.1 Attention in ASD

Sustained attention, or vigilance, is the ability to voluntarily maintain the focus of attention towards infrequently occurring critical events (Parasuraman and Yantis, 1998). It is not only a measure of attentional processes but also of impulsivity and is involved in other executive processes such as inhibitory control (Bari and Robbins, 2013). Sustained attention has also been described as a decrement of vigilance over time, a concept that has been influential in the literature of other neurodevelopmental disorders, namely ADHD (Oosterlaan et al., 1998).

A typical paradigm for indexing sustained attention is the Continuous Performance Test (CPT) (Rosvold et al., 1956). This task requires maintaining attention to a series of rapidly occurring stimuli in order to respond to an infrequently occurring stimulus (Eliason and Richman, 1987) and is commonly characterised by the rapid presentation of continuously changing stimuli with an instructed target stimulus or pattern (Riccio et al., 2002). Another variant of sustained attention tasks are psychomotor vigilance tasks requiring a motor response to a stimulus after unpredictable or predictable delays (Drummond et al., 2005). A version of this task is described at length in Chapter 5.

Inattention is a behavioural/cognitive phenotype which has been consistently associated with ASD (Allen and Courchesne, 2001, Sturm et al., 2004). It has been suggested that attention impairments may underlie some of the primary symptoms in ASD (Courchesne et al., 1989, Wainwright-Sharp and Bryson, 1993), although such early theories of attention impairment have been disputed (Garretson et al., 1990, Minshew et al., 1992). There is relatively consistent neuropsychological evidence for sustained attention impairments in autism (Garretson et al., 1990, Allen and Courchesne, 2001, Schatz et al., 2002, Corbett and Constantine, 2006, Corbett et al., 2009, Murphy et al., 2014, Chien et al., 2015), albeit with some studies finding no differences between participants with ASD and typically-developing individuals (Pascualvaca et al., 1998, Johnson et al., 2007). Many studies have linked attention-related neurocognitive difficulties in individuals with ASD to the specificity, complexity or motivational salience of task stimuli (Garretson et al., 1990, Courchesne et al., 1994, Pierce et al., 1997, Pascualvaca et al., 1998, Mann and Walker, 2003, Corbett and Constantine, 2006). Moreover, attempts have been made to classify clinical subtypes of ASD based on the presence/absence of attention-related symptomatology (Bonde, 2000), and one study identified that 95% of a sample of children with ASD exhibited attention problems, and 50% had problems with impulsivity (Sturm et al., 2004).

Two studies have also found that sustained attention functions in ASD improve with age (Murphy et al., 2014, Chien et al., 2015). Moreover, Geurts and colleagues suggested that poor performance of individuals with ASD on tasks designed to measure cognitive flexibility in the context of cognitive control, such as the intradimensional-extradimensional shift task, may be more closely related to neurocognitive deficits in sustained attention, as subjects must maintain attention across the task to identify 'switch' trials (Geurts et al., 2009). As with much of the neurocognitive literature

investigating individuals with ASD, it should be noted that groups of ASD individuals investigated in these studies are widely heterogeneous, indicating that performance differences (or lack thereof) could be due to comorbid symptoms related to inattention, ADHD (Tye et al., 2014) or ASD symptom severity.

1.3.2 Attention in OCD

Attentional priority to obsessions and anxieties has been suggested as a key maintaining factor of OCD (Salkovskis, 1985). Thus, it would make sense that individuals with OCD show impairments on neurocognitive assessments of attention to external stimuli. However, collective research has produced somewhat mixed findings. Studies have most commonly used the CPT to investigate sustained attention in OCD, but most work has been in adult populations. Both paediatric and adult studies have reported no behavioural differences between patients and controls (Rosvold et al., 1956, Nordahl et al., 1989, Zielinski et al., 1991, Rapoport et al., 1992, Martin et al., 1993, Aronowitz et al., 1994, Milliery et al., 2000), while other studies provide evidence for attentional disturbances in adults with OCD (Gordon, 1985, Mataix-Cols et al., 1997, Schmidtke et al., 1998, Penadés et al., 2005) during controlled (Schmidtke et al., 1998), selective (Penadés et al., 2005) and sustained attention (Mataix-Cols et al., 1997).

Early evidence did not provide convincing support for attentional disturbances in OCD, showing mixed results on tasks of information processing speed and selective attention, and no differences between patients and controls on visual attention, attention span and sustained attention tasks (Zielinski et al., 1991, Mataix-Cols et al., 1997, Milliery et al., 2000). An initial review suggested that there is little evidence for sustained attention impairments in OCD across the lifespan (Kuelz et al., 2004). However, a more recent meta-analysis of 115 adult studies reported a medium effect size for sustained attention deficits in OCD (Abramovitch et al., 2013). Moreover, a

recent review (Benzina et al., 2016) suggested that sustained attention is the second-most studied domain of attention in OCD after focused attention and found that although one included study (Rao et al., 2008) showed no evidence for sustained attention deficits in OCD, the majority of studies (including a meta-analysis of 17 studies) using the CPT (Aigner et al., 2007, Trivedi et al., 2008, Shin et al., 2014), and related tasks (Morein-Zamir et al., 2010, Rajender et al., 2011, Bersani et al., 2013) found a sustained attention deficit in OCD individuals. Moreover, this review (Benzina et al., 2016) also supports a trend in the OCD literature toward a deficit in focused attention, supported by previous meta-analyses (Shin et al., 2014, Snyder et al., 2014).

1.3.3 Summary of attention functions in ASD and OCD

Sustained attention has been investigated in the neurocognitive literature of both ASD and OCD, resulting in somewhat mixed findings, particularly in OCD. Despite the fact that clinically, ASD is commonly associated with symptoms of inattention (Sturm et al., 2004), some neurocognitive studies of sustained attention in ASD have shown no behavioural differences between ASD individuals and typically-developing controls (Pascualvaca et al., 1998, Johnson et al., 2007). However, the majority of studies do support sustained attention impairments in both adults and adolescents with ASD (Garretson et al., 1990, Allen and Courchesne, 2001, Schatz et al., 2002, Corbett and Constantine, 2006, Corbett et al., 2009, Murphy et al., 2014, Chien et al., 2015), providing relatively consistent evidence that at the neurocognitive level, there is an underlying impairment in ASD individuals' ability to maintain attention toward infrequently occurring stimuli, possibly linked to the specificity or motivational salience of the task (Courchesne et al., 1994, Corbett and Constantine, 2006).

In OCD, neurocognitive results are less consistent, with the disorder not typically associated with clinical symptoms of inattention, and many studies reporting

no neurocognitive performance impairments in individuals with OCD (Rosvold et al., 1956, Nordahl et al., 1989, Zielinski et al., 1991, Rapoport et al., 1992, Martin et al., 1993, Aronowitz et al., 1994, Milliery et al., 2000), while many other studies report impaired attention across various domains in patients relative to controls (Gordon, 1985, Mataix-Cols et al., 1997, Schmidtke et al., 1998, Penadés et al., 2005). However, many of these studies have been in adults with OCD, so less is known about findings in paediatric populations. While early neurocognitive theories did not support deficits in sustained attention in OCD, more recent reviews (Benzina et al., 2016) support impaired attention functions, and abnormal attention to external information seems to conceptually fit with clinical characteristics in ASD and OCD. I.e., ASD individuals have heightened attention toward specific interests and rituals, and OCD individuals have heightened attention towards internally generated obsessions, in both instances focusing less on seemingly 'unimportant' external information. Thus, further investigation of sustained attention abnormalities in both disorders is warranted. Moreover, given the fact that both disorders have shown neurocognitive deficits in sustained attention, understanding the neural underpinnings of these deficits and the degree to which they are shared or disorder-specific may help elucidate similarities and differences in the biological basis of trans-diagnostic neurocognitive impairments in each disorder. Sustained attention in ASD and OCD is discussed further in Chapter 5.

1.4 Reward-related decision-making

1.4.1 Temporal discounting and related functions in ASD

Temporal discounting (TD) is a measure of impulsive reward-based decision-making, defined as the rate at which a reward is subjectively discounted when its attainment is delayed in time. Thus, temporal foresight is one's ability to forego an

immediately available reward in favour of a larger but delayed reward (Rubia et al., 2009a). TD is a stable, trait-like measure of choice impulsivity (Kirby, 2009), matures with age (Christakou et al., 2011), and is more impaired in impulsive individuals (Rubia et al., 2009a, Noreika et al., 2013). As such, impulsivity has been conceptualised as a behavioural style involving premature and inadequate decisions where responses are made early and without full consideration of any consequences (Rubia et al., 2000, Smith et al., 2002) and is critically linked to impairments in temporal foresight.

Tasks assessing TD require choices between small, immediate rewards and larger, delayed rewards (Richards et al., 1997, Christakou et al., 2011). In individually-adjusted TD paradigms (Richards et al., 1997, Christakou et al., 2011), the immediate reward is adjusted using an algorithm based on previous choices of the participant for different delays to narrow the range of immediate values offered for each delay type, converging towards the value of the participant's subjective equivalent of the fixed delayed reward (Richards et al., 1999). From this, a delay discounting function can be calculated which is typically hyperbolic and the steepness of which indicates the individual TD rate, which is associated with impulsivity (Richards et al., 1999, Critchfield and Kollins, 2001). Further explanation of TD tasks and characterisation of task performance is described in Chapter 6.

Despite the implication of impulsivity in the associated symptom domains of ASD (Fineberg et al., 2009), there have been relatively few studies investigating TD in ASD (Antrop et al., 2006, Demurie et al., 2012, 2013, Chantiluke et al., 2014b, Faja and Dawson, 2015). One study in young children (6-7 years old) (Faja and Dawson, 2015) found that ASD individuals behaved more impulsively on a version of the TD task adapted for children. 40% of the children with ASD did not wait the full 15-minute delay to receive a larger, later reward and instead opted to take the smaller, sooner

reward. Moreover, of the participants that chose the smaller, sooner reward, ASD children waited significantly less time compared to typically-developing children before choosing to take the reward, in line with findings from the same study that parents of ASD individuals reported lower levels of effortful control in their children compared to parents of typically-developing children. This is in line with a recent study in adolescents with ASD and with comorbid ASD and ADHD which found that these two groups discounted rewards more steeply compared to control participants on a computerised TD task (Chantiluke et al., 2014b). Conversely, another study in children and adolescents with ASD (Demurie et al., 2012) found that on a TD task with monetary rewards, ASD individuals showed the same rate of discounting compared to their typically-developing peers and adolescents with ADHD. This finding is in line with an earlier study showing similar comparable TD performance between children with high-functioning autism and typically-developing controls (Antrop et al., 2006).

Successful TD also depends on intact reward-motivated planning and action selection behaviour. ASD adults and children have been shown to have neurocognitive impairments during planning tasks (Ozonoff et al., 1991, Ozonoff and McEvoy, 1994, Ozonoff and Jensen, 1999, Geurts et al., 2004, Hill, 2004), implying difficulties with forward-thinking behaviour necessary for TD. Moreover, it has been suggested that individuals with ASD exhibit deficits in top-down cognitive control that is key in the ability to delay impulsive decisions in the immediate future in favour of a more beneficial outcome later in time (Dalley et al., 2011). During decision-making, it has been shown that children with ASD have deficits with response selection and monitoring compared to typically-developing children and children with ADHD, but that this ability improves with age (Happé et al., 2006). Reduced salience of social stimuli has also been implicated in reward-based decision-making in ASD (Dawson et al., 2012), in line with the social motivation theory (Chevallier et al., 2012), suggesting

that ASD individuals are less able to assign reward values to social stimuli. This idea is supported by the findings of Demurie and colleagues (Demurie et al., 2013), who investigated whether ASD individuals discounted monetary vs. material rewards at different rates. They found that while there was no overall difference between ASD children and typically-developing children, ASD individuals, but not typically-developing individuals, discounted material rewards more steeply than monetary rewards, suggesting a domain-specific effect of TD in children with ASD linked to differences in reward valuation of affectively-salient stimuli.

1.4.2 Gambling and reward learning in ASD

Reward-related decision-making has been widely studied within the context of gambling, and more specifically, the Iowa Gambling Task (IGT) (Bechara et al., 1994, Bechara et al., 1997). The IGT involves reward-based decision-making and reinforcement learning to obtain reward in the face of positive and negative feedback. Participants must learn to forego immediately high-reward options that ultimately lead to long-term losses (risky/disadvantageous choices) in order to choose options with more modest immediate rewards that ultimately lead to a long term gain (safe/advantageous choices). Apart from reinforcement learning and reward-based decision-making, the task also measures temporal foresight, requiring an understanding of future long-term consequences of current choices and the ability to inhibit the "thrill" of an immediate reward, i.e. motivation control. A more complete description of the IGT is provided in Chapter 7. Performance on the IGT improves with age (Blair et al., 2001, Huizenga et al., 2007, van Duijvenvoorde et al., 2010, Christakou et al., 2013a), and among adolescent populations, is independent of the development of working memory or motor inhibition (Hooper et al., 2004).

Five studies have used traditional versions of the IGT in ASD (Johnson et al., 2006, Yechiam et al., 2010, South et al., 2014, Mussey et al., 2015, Zhang et al., 2015b). The majority of these studies found that adults (Mussey et al., 2015) and children/adolescents (Johnson et al., 2006, Yechiam et al., 2010) with ASD are less consistent in their choices, switching more frequently between decks, possibly due to difficulties with implicit learning where subjects are required to learn through repeated choices without explicit reference to the learning rule (Johnson et al., 2006). This theory is further supported in Scott-Van Zeeland et al.'s study showing impaired implicit learning during a reward learning task (Scott-Van Zeeland et al., 2010a) and another study showing that adults with ASD exhibit learning deficits which impair their ability to establish an effective reward-based working memory to drive decisions (Solomon et al., 2015).

Another study using the IGT in adults found that ASD individuals relative to control participants preferred risky decks, providing further evidence for reward-based learning deficits in ASD (Zhang et al., 2015b). However, impaired performance and learning on the IGT is not consistent, as one study found slower learning rates but equivalent overall performance in adolescents with ASD relative to typically-developing controls (Yechiam et al., 2010), while another paediatric study found similar overall performance but improved learning in the ASD group relative to controls (Johnson et al., 2006). Moreover, three paediatric studies in ASD children using adapted versions of the IGT (e.g. as outlined in (Kerr and Zelazo, 2004)) showed no difference in the number of risky choices between ASD children and typically-developing children (South et al., 2008, Faja et al., 2013, Gonzalez-Gadea et al., 2016), and a later study from South and colleagues (South et al., 2014) found superior overall performance across the task in adolescents with ASD relative to control participants. One hypothesis for this superior performance is that ASD adolescents have elevated loss avoidance

(South et al., 2014), as opposed to risky reward seeking behaviour that is usually observed in typically-developing adolescent populations (Smith et al., 2012).

Reversal learning tasks also involve reinforcement-based implicit learning and cognitive flexibility required in the IGT (Chantiluke et al., 2015a). Children with ASD have been shown to have poor performance on reversal learning tasks (McEvoy et al., 1993, Coldren and Halloran, 2003, Yerys et al., 2007, Loveland et al., 2008, Zalla et al., 2009), but a more recent study showed that adolescents with ASD had performance statistically similar to that of typically-developing controls (Chantiluke et al., 2015a), although ASD boys did make numerically more errors. Comparable reward learning between ASD individuals and controls has also been found in adults with ASD (Johnson et al., 2006, Panasiti et al., 2016), and a study investigating reward-motivated attention (Schmitz et al., 2008) similarly found comparable performance between ASD adults and control participants when presented with monetary incentives.

1.4.3 Temporal discounting and related functions in OCD

There are multiple hypotheses supporting impaired decision-making in OCD. Graybiel and Rauch initially proposed that OCD results from maladaptive habit learning involving impaired stimulus-response associations, underpinned by deficits in orbitofrontal-basal ganglia circuitry (Graybiel, 2000). Cognitive theories suggest that symptoms arise as a result of disordered action valuation during decision-making; compulsions are purposeful, goal-driven acts to generate temporary and rewarding relief from anxiety caused by obsessions (Salkovskis, 1985, Rachman, 1997, Cavedini et al., 2006). More recent work has suggested that compulsions persist because of a lack of control over goal-directed decisions, which results from an imbalance between goal-directed and habit-based learning systems in OCD (Gillan and Robbins, 2014).

Despite the fact that OCD has been characterized as a disorder of impaired decision-making underpinned by orbitofronto-striatal dysfunction (Sachdev and Malhi, 2005), only two previous studies (Vloet et al., 2010, Pinto et al., 2014) have specifically investigated TD in OCD and did not find behavioural differences between adults (Pinto et al., 2014) or adolescents (Vloet et al., 2010) with OCD and control participants. However, studies using tasks tapping other temporal-foresight related functions have provided some evidence of abnormalities in OCD. For example, Cavedini and colleagues proposed that poor performance during reward-based decision-making tasks is driven by adult patients' motivation for immediate reward, suggesting that OCD patients are less sensitive to long-term consequences (Cavedini et al., 2002), a characteristic that may translate to temporal foresight abilities. This impaired decision-making and response inhibition in adult OCD may be related to a poor ability to control and inhibit repetitive, compulsive behaviours and intrusive obsessions (Olley et al., 2007). Lastly, individuals with OCD also show poor performance on planning tasks (van den Heuvel et al., 2011, Shin et al., 2014), related to forward-thinking behaviour important for successful TD.

1.4.4 Gambling and reward learning in OCD

Individuals with OCD have neurocognitive deficits in goal-directed adaptive behaviours including behavioural flexibility, particularly in the context of altered or uncertain environments or outcomes (Chamberlain et al., 2007b, Gu et al., 2008, Page et al., 2009, Zhang et al., 2015a). Moreover, comorbidity rates of so-called 'behavioural addictions' (Holden, 2001) such as pathological gambling with OCD have been estimated to be as high as 20% (Dell'Osso et al., 2006). These abnormalities and maladaptive compulsive behaviours are though to stem, at least in part, from impaired reward-processing underpinned by orbitofronto-striatal dysfunction (Sachdev and

Malhi, 2005, Cavedini et al., 2006, Figee et al., 2011) and a disrupted balance between goal-directed versus habit systems (Gillan et al., 2011).

The majority of behavioural studies using gambling tasks thought to tap frontal lobe, and more specifically orbitofrontal, dysfunction in OCD show impaired performance in patients relative to controls (Purcell et al., 1998, Cavedini et al., 2002, Cavallaro et al., 2003, Fullana et al., 2004, Olley et al., 2007, Starcke et al., 2010, Rocha et al., 2011, Kodaira et al., 2012, Grassi et al., 2015), although only one of these studies has been in children (Kodaira et al., 2012). However, Nielen and colleagues found comparable decision-making behaviour in adult patients vs. controls (Nielen et al., 2002), in line with similar negative findings during gambling under risk (Chamberlain et al., 2007a, Hybel et al., 2016). A large study in unmedicated adolescents with OCD found comparable performance on "hot" EF tasks of motivated decision-making in patients compared to controls (Hybel et al., 2016). However, this study investigated decision-making under risk and suggested that, in line with the findings of (Kim et al., 2015a) and (Zhang et al., 2015a), decision-making under ambiguity, as in the IGT, may be a better construct within which to investigate reward-based decision-making impairments in OCD. Intact reward processing is also responsible for appropriate responses during reward (or punishment) outcomes during incentive-based learning. In OCD, impaired reward processing and maladaptive behaviours are thought to be an effect of abnormal development of goal-directed learning (Cavedini et al., 2006, Gillan and Robbins, 2014). However, two early studies in adults with OCD found no behavioural impairments during implicit learning relative to controls, as evidenced by intact performance on the serial reaction time implicit sequence learning task (Rauch et al., 1997a, Deckersbach et al., 2002).

This evidence collectively suggests heightened impulsivity, risky decision-making and reward system dysfunction in OCD. This is seemingly contrary to clinical representations of risk-aversion and doubtfulness that are commonly associated with OCD and indeed seems to fit more with the clinical phenotype of addiction (Grassi et al., 2015), leading some to suggest whether OCD may be considered a type of "behavioural addiction" (Denys et al., 2004, Figee et al., 2011).

1.4.5 Summary of reward-related decision-making in ASD and OCD

Although results in the neurocognitive literature are somewhat mixed, abnormal goal-driven learning seems to be associated with ASD (Johnson et al., 2006) and OCD (Gillan and Robbins, 2014). Both disorders also seem to be impaired during tasks of planning (Hill, 2004, Shin et al., 2014), a function especially important for forward-thinking behaviour during reward-based decision-making and TD. Discrepancies in findings could be due to different deficits among different age groups, as few studies have looked across the lifespan from adolescence into adulthood and tend to focus instead on either adolescents or adults, with the majority of studies in adults. Nonetheless, impaired reward-based decision-making seemingly fits with the clinical pictures of both ASD and OCD, as it has been suggested that in ASD, motivational salience of rewards, particularly social rewards (Dawson et al., 2012), is abnormal, while compulsions in OCD have been associated with insufficient feelings of reward, leading to "not just right" feelings (Fineberg et al., 2009). Moreover, the question in the OCD literature of whether symptoms arise from abnormal outcome valuation or whether they result from dysfunctional goal-directed learning and decision control (Gillan and Robbins, 2014) could be extended to ASD in the investigation of neuropsychological profiles driving decision-making that may maintain repetitive behaviours in these disorders. However, no studies have compared reward-based

decision-making between these disorders. A better understanding of performance differences or similarities between disorders would elucidate the degree to which similarities in cognitive impairments are shared and/or disorder-specific behavioural phenotypes.

1.5 Other cognitive domains

1.5.1 ASD

In order to gain a complete and comprehensive view of the neuropsychological profiles of both ASD and OCD, two complex and heterogeneous disorders, it is important to consider additional aspects of cognitive domains within each disorder. Here, working memory will be reviewed briefly, as studies have implicated WM functions in attention and reward-based decision-making, specifically TD (Shamosh et al., 2008, Wesley and Bickel, 2014). Additional domains of cognitive impairment particularly relevant to ASD will also be briefly discussed.

Working memory impairments, specifically in the domain of visuo-spatial WM, have been consistently shown in children and adolescents with ASD (Bennetto et al., 1996, Russell et al., 1996, Minshew et al., 1999, Minshew and Goldstein, 2001, Joseph et al., 2005a, Joseph et al., 2005b, Landa and Goldberg, 2005, Williams et al., 2005, Nakahachi et al., 2006, Verte et al., 2006, Williams et al., 2006, Luna et al., 2007, Steele et al., 2007, Loveland et al., 2008, Cui et al., 2010, Zinke et al., 2010, Fried et al., 2016), although there have been some studies showing no impairments (e.g. (Griffith et al., 1999, Ozonoff and Strayer, 2001, Chantiluke et al., 2014a)). Such discrepancies are perhaps due to the wide heterogeneity across ASD as well as variations in task difficulty that is common among different WM tasks, and it has been suggested that individuals

with ASD are impaired specifically on more complex (versus simpler) tasks of WM (Vogan et al., 2014).

While it is clear that children and adolescents with ASD exhibit executive dysfunction and that such impairments play a vital part in the overall aetiology of the disorder (Hughes et al., 1994, Geurts et al., 2004, Hill, 2004, Ozonoff et al., 2004, Corbett et al., 2009), the autism spectrum has been perhaps most consistently associated with deficits in social and communication difficulties. ASD individuals are impaired in Theory of Mind (ToM), or mentalising, defined as the ability to comprehend and empathize with the mental state of others (Baron-Cohen et al., 1985, Frith, 1994, Baron-Cohen, 2001, Joseph and Tager–Flusberg, 2004, Tager-Flusberg, 2007). ASD has also been associated with deficits in central coherence, that is, the ability to assess information as a whole on a global scale and focus less on finer minute details in order to understand the more general meaning or context of a situation. ASD children have been shown to have superior perception of local features relative to typically-developing children (Shah and Frith, 1983). Such "weak" central coherence has been suggested to play a key role in the clinically-observed symptoms of ASD (Happé, 1997, Happé and Frith, 2006, Pellicano et al., 2006, Booth and Happé, 2010).

1.5.2 OCD

Although EF abnormalities are consistently implicated in the pathophysiology of OCD (Menzies et al., 2007), findings of WM impairments are mixed at best, and indeed are less consistent than in the ASD literature. WM has been widely studied in adults with OCD (e.g. (Purcell et al., 1998, van der Wee et al., 2003, van der Wee et al., 2007, Nakao et al., 2009a), reviews: (Chamberlain et al., 2005, Melloni et al., 2012)), but there are far fewer studies of this cognitive domain in adolescents with OCD (Diwadkar et al., 2015), with a small preliminary study showing no behavioural impairments in

WM (Ornstein et al., 2010), supported by a larger study in adults (Nakao et al., 2009a). One study in adults showed that visuo-spatial WM deficits were more pronounced in OCD patients under conditions of uncertainty (Lambrecq et al., 2014), and WM performance has been associated with specific subtypes of OCD, namely checking behaviour (Jaafari et al., 2013). However, a comprehensive review concluded that WM impairments may be secondary to broader EF dysfunction in OCD (Harkin and Kessler, 2011).

1.6 Overall summary and conclusions

This chapter has reviewed the neurocognitive literature in ASD and OCD concerning cognitive control, attention and reward-based decision-making, as well as briefly reviewing other cognitive domains that are relevant to these constructs or disorders. It is somewhat difficult to compare across studies, as there is vast heterogeneity within samples and between studies in terms of symptom domains and severity, medication and treatment, illness duration, and age, possibly explaining at least some of the inconsistency in findings. However, keeping these caveats in mind, it seems that further investigation of neuropsychological behaviour during cognitive control, sustained attention and reward-based decision-making is warranted. Many studies have shown deficits in these functions in ASD and OCD (Hughes et al., 1994, Hill, 2004, Menzies et al., 2008, Fineberg et al., 2009, Ornstein et al., 2010, Nakao et al., 2014), but no studies have compared EF between these disorders. Moreover, hot EF and decision-making deficits have been shown more consistently to be impaired in OCD than cool EF deficits (Abramovitch et al., 2015a), so it is important to better understand the neural underpinning of these abnormalities in OCD and how they relate to ASD to determine the extent to which deficits are shared or disorder-specific. Examining the underlying neurofunctional mechanisms of EF in ASD and OCD and whether they are shared or

disorder-specific is a critical aspect of studying biologically-based markers that may be shared between or distinct to these disorders. Moreover, the investigation of these functions in adolescent samples is especially important. Despite the fact that both ASD and OCD most commonly develop in childhood or adolescence, the majority of studies, particularly in OCD, have been conducted in older samples.

Widespread EF deficits have been found in children with ASD, with early theories suggesting that autism is a disorder of executive dysfunction (Russell, 1997, Hill, 2004). Children with ASD have relatively consistent deficits in impulsivity-related tasks of planning, cognitive control and TD (Solomon et al., 2008), while it has also been suggested that ASD individuals exhibit key features of compulsive behaviours (Fineberg et al., 2009), though no studies have compared individuals with ASD and with OCD to formally test this. However, in contrast to OCD, ASD is also closely related to deficits in social communication, implicating socio-emotional processing abnormalities that should be considered when thinking about abnormal emotionally charged 'hot' EF such as reward-based decision-making.

It has been suggested that adults with OCD have neuropsychological deficits in a range of non-emotional 'cool' EF functions including working memory, attention and cognitive control (Abramovitch et al., 2013, Nakao et al., 2014, Shin et al., 2014, Snyder et al., 2014), but there have been far fewer studies in paediatric OCD, and a recent preliminary meta-analysis based on this limited research base of 11 studies found only small, non-significant effect-sizes for EF subdomains of 'cool' functions including set-shifting and planning and no differences on WM and inhibition (Abramovitch et al., 2015a), supported by a more recent study finding no deficits in children/adolescents with OCD on a range of cool and hot EF tasks (Hybel et al., 2016). This suggests that many cool EFs such as inhibitory control may be unaffected in children with OCD

(Ornstein et al., 2010). Evidence from studies of hot EF in adult OCD suggests that impairments in decision-making may result from an imbalance between goal-directed and habit-based learning systems (Chamberlain et al., 2005, Olley et al., 2007, Gillan and Robbins, 2014, Nakao et al., 2014, Zhang et al., 2015a), although this has been refuted by neurocognitive work specifically investigating children with OCD (Hybel et al., 2016). Heterogeneity in task types and participant characteristics may be partially to blame for these inconsistencies, but evidence specifically in child and adolescent populations may also suggest developmental effects on EF deficits in OCD. Some evidence suggests differences in neuropsychological functioning between children/adolescents with OCD and adults with OCD, possibly providing support for a specific neurodevelopmental subtype of OCD (Ornstein et al., 2010, Abramovitch et al., 2015a).

In summary, there is evidence to suggest that both hot and cool EF difficulties in cognitive control, attention and reward-based decision-making are present in both ASD and OCD. However, no studies have compared these disorders on the basis of these impairments. Overall, evidence points towards impairments in cognitive control in both ASD and OCD. ASD-related impairments may be linked to impulsive and repetitive behaviours (Yerys et al., 2009) and seem to be more specific to motor inhibition (Hill, 2004, Bishop and Norbury, 2005, Verte et al., 2005, Christ et al., 2007, O'Hearn et al., 2008, Sanders et al., 2008, Lemon et al., 2011, de Vries and Geurts, 2014) and switching (Ozonoff et al., 1991, Hughes et al., 1994, Ozonoff and McEvoy, 1994, Ozonoff, 1995, Bennetto et al., 1996, Ozonoff et al., 2000, Verte et al., 2005, Yerys et al., 2009, Van Eylen et al., 2011, Yerys et al., 2011, Landry and Al-Taie, 2016, Westwood et al., 2016, Yeung et al., 2016), as studies have shown that interference inhibition is relatively intact in ASD (Ozonoff and Jensen, 1999, Russell et al., 1999, Christ et al., 2007, Adams and Jarrold, 2009, Christ et al., 2011). OCD individuals have

also shown impairments in motor inhibition (Chamberlain et al., 2006, Penadés et al., 2007, Boisseau et al., 2012, Kang et al., 2013, Morein-Zamir et al., 2014, Sohn et al., 2014) and interference inhibition (Bannon et al., 2002, Nabeyama et al., 2008, Nakao et al., 2009b, Schlösser et al., 2010) and switching (Britton et al., 2010), with less known about abnormalities during interference inhibition. However, such cognitive control deficits hypothetically fit with proposed clinical models of OCD which suggest that symptoms results from failed top-down inhibitory control mechanisms (Fineberg et al., 2009, van Velzen et al., 2014).

It seems that abnormalities in attentional processes are implicated in ASD and OCD, but it may be that individuals with ASD are more sensitive to the social or emotional context of attention-capturing stimuli (Garretson et al., 1990, Courchesne et al., 1994, Pierce et al., 1997, Pascualvaca et al., 1998, Mann and Walker, 2003, Corbett and Constantine, 2006), while impairments in OCD may be related to the distraction of internally generated thoughts and obsessions (Salkovskis, 1985, Shin et al., 2014, Snyder et al., 2014) as well as older subtypes of the disorder (Ornstein et al., 2010, Abramovitch et al., 2015a).

Reward-based hot EF and decision-making also seem to be impaired in both disorders, although theories explaining the underlying basis of these impairments are inconsistent. It may be that while both disorders have difficulties with forward-thinking behaviour and planning that drives decision-making (Geurts et al., 2004, Hill, 2004, van den Heuvel et al., 2011, Shin et al., 2014), this behaviour in ASD in underpinned by heightened impulsivity (Fineberg et al., 2009, Chantiluke et al., 2014b, Faja and Dawson, 2015), while in OCD it may be underpinned by abnormal reward valuation (Salkovskis, 1985, Rachman, 1997, Cavedini et al., 2006) or imbalance between goal-directed and habit-based systems (Gillan and Robbins, 2014). This thesis conducts a

comparative meta-analysis of cognitive control studies and compares adolescents with ASD and with OCD to test these hypotheses and understand the differences and similarities in the brain systems that underpin these cognitive functions.

CHAPTER 2 - BRAIN STRUCTURE ABNORMALITIES IN ASD AND OCD

2.1 Introduction

The previous chapter reviewed evidence from the neuropsychological literature showing that children with ASD and those with OCD may have overlapping deficits in a wide range of executive functions including sustained attention, temporal foresight, reward-based decision-making and inhibitory control. This chapter will introduce basic principles behind structural brain imaging techniques and review the structural brain abnormalities in each disorder that may underpin neuropsychological deficits.

Historically, it was observed that individuals with lesions to regions in the prefrontal cortex (PFC) exhibited deficits in EF. Such observations led to the theory that the underlying neural basis of EF problems might exist in prefrontal cortical areas of the brain (Miller and Cohen, 2001). As cognitive and behavioural impairments seen in these early case studies seemed similar to abnormalities observed in psychiatric disorders such as ASD and OCD, scientists began to hypothesise that cognitive phenotypes associated with these disorders may be related to abnormalities in the PFC. However, the only way to examine these associations between brain abnormalities and cognitive function or symptoms in-vivo is through the use of neuroimaging techniques, which allow the imaging and measurement of structure, function and biochemistry of the brain. Such methods have grown exponentially, from initial methods of post-mortem and lesion studies, to the first use of Computerised Tomography (CT) in the 1970s (Ambrose, 1973, Hounsfield, 1973), to modern methods of magnetic resonance imaging (MRI) (Hoeffner et al., 2012). Today, the only way of obtaining structural information about the brain using non-invasive or non-radiating procedures is through structural MRI (sMRI) (Poldrack et al., 2011).

2.1.1 Magnetic resonance imaging to investigate brain structure

sMRI has greatly advanced our understanding of brain anatomy and how it might relate to higher cognitive function. MRI (Damadian, 1971) relies on the basic magnetic properties of the different components in brain tissue. Protons in different tissues contain different magnetic properties, and a set magnetic field of an MRI scanner (e.g. 3 Tesla) enables the alignment of these particles in the direction of the field (Higgins et al., 1996, Banich, 2004, Symms et al., 2004). When a subject is placed within the magnetic field of an MRI scanner, the protons within various tissues align in the direction of the scanner's magnetic field. The scanner then emits short radio-frequency pulses which change the magnetic field and force the protons to temporarily align with a new field. The time it takes for the protons to re-align with the original field after the pulse is known as the "relaxation time" (termed T_1 and T_2) and is important for the eventual 3D reconstruction of a brain image (Higgins et al., 1996). The main advantage of MRI over other modern methods such as CT is the superior spatial resolution of MRI and the lack of need for X-rays. However, as the MRI scanner involves strong magnetic fields, this introduces the relative disadvantage that people with metal in their bodies (e.g. surgical pins, dental work etc.) often cannot be scanned with MRI. Moreover, the space where the subject lies in an MRI scanner (the "bore") is quite small, so participants, particularly children, often become claustrophobic. The sounds created by the radio-frequency pulses and other scanner functions are also quite loud, making the scan uncomfortable for some participants.

The two main tissue types measured by sMRI are white and grey matter. White matter refers to the myelinated axon bundles extending from a neuron's cell body, whereas grey matter is the cell body itself (Kandel et al., 2000). Grey matter density and volume is most commonly measured with standard sMRI. Developmental research has

shown a maturation pattern of grey matter that follows an inverted U-shape, increasing with age throughout childhood, peaking in adolescence and declining throughout adulthood (Blakemore and Choudhury, 2006, Giedd and Rapoport, 2010). While the actual number of neurons changes very little in development, this pattern of maturation has been attributed to the proliferation of synaptic connections between existing neurons and the later synaptic "pruning" in adolescence into adulthood, as the necessity of information transfer is refined across development. Thus, development encompasses not only the improved efficiency by which the brain transfers information, but also a refinement of the information being transferred. Certain fronto-striatal and fronto-cerebellar brain regions such as the PFC, and more specifically the dorsolateral PFC (DLPFC), as well as BG and cerebellum have been shown to develop later than subcortical limbic areas (Casey and Jones, 2010, Tiemeier et al., 2010). A linear relationship has been shown between structural brain development (particularly in prefrontal cortical regions) and the development of cognitive and executive functions (Blakemore and Choudhury, 2006, Casey and Jones, 2010, Giedd and Rapoport, 2010). Therefore, an understanding of the structural characteristics of the adolescent brain in ASD and OCD is critical for a complete understanding of the underpinnings of cognitive features of these disorders.

2.2 Brain structure abnormalities

2.2.1 Brain structure abnormalities in ASD

A landmark hypothesis that abnormally large brain size may be a structural feature of autism was first suggested in 1943 by Leo Kanner in a series of case studies (Kanner, 1943). This paper reported that 5 of 11 cases had unusually "large heads". This study was an initial qualitative observation of this feature, but further quantitative

research has shown that between 20% and 40% of individuals with ASD have a head circumference within the 97th percentile, known as macrocephaly (Acosta and Pearl, 2004, Mosconi et al., 2006, Verhoeven et al., 2010, Stigler et al., 2011). However, the actual brain structure of individuals with ASD could not be incorporated into this hypothesis without the use of sMRI.

An early and critically important study in the brain structure of children with ASD was a longitudinal investigation by Courchesne and colleagues (Courchesne et al., 2001a) which found that at birth, 30 boys had a normal head circumference, but by age 2-4 years, 90% who developed ASD had a head circumference larger than average, and 37% of those qualified as macrocephalic. Moreover, this study found that at ages 2-3 years, ASD boys had larger than normal cerebral grey (12%) and white (18%) matter volumes, as well as cerebellar white matter volumes (39%). Moreover, this abnormality was no longer present later in life when the 30 autistic boys were scanned at age 12-16 years, suggesting that autism may be characterised by early brain overgrowth followed by abnormally slowed brain growth later in life, leading to relative normalisation by adolescence (Courchesne et al., 2001a).

This trajectory finding has been replicated (Courchesne et al., 2003, Hazlett et al., 2005, Redcay and Courchesne, 2005, Lange et al., 2015), and a number of studies support increased total brain volume (TBV) (Sparks et al., 2002, Mak-Fan et al., 2012, Nordahl et al., 2012) as well as enlarged grey (Calderoni et al., 2012, Mak-Fan et al., 2012) and white matter during early life specifically in frontal and temporal regions (Courchesne et al., 2004). Most of this evidence comes from studies in young children aged 2-5 years, and this timeframe of proposed early brain overgrowth and the study of structural abnormalities in the autistic brain is of particular importance within the context of the emergence of autistic traits and clinical symptoms, which generally

begins around 2.5 years (American Psychiatric Association, 2013). Nonetheless, ASD is a highly heterogeneous condition, and other studies across development have found increased TBV, grey and white matter volumes in both adolescents and adults with ASD (Piven et al., 1992, Brambilla et al., 2003, McAlonan et al., 2005, Palmen et al., 2005a, Hazlett et al., 2006, Stanfield et al., 2008, Brun et al., 2009) which brings the above proposed growth trajectory into question. It is possible that focus on more consistent study design and subgroups of specific profiles of ASD are needed as well as large-scale longitudinal studies across development.

Regarding whole-brain studies investigating structural abnormalities in children and adolescents with ASD relative to typically-developing controls, increased TBV has been observed (Sparks et al., 2002, Waiter et al., 2004, Carper and Courchesne, 2005, Palmen et al., 2005b, Hazlett et al., 2006, Brun et al., 2009, Mitchell et al., 2009, Stigler et al., 2011), and increased grey matter volumes (GMV) have been found in frontal regions including inferior frontal cortex (IFC), DLPFC, medial PFC (mPFC), anterior cingulate cortex (ACC) and left medial and superior frontal cortex (Waiter et al., 2004, Bonilha et al., 2008, Ke et al., 2008, Calderoni et al., 2012, DeRamus and Kana, 2015, Foster et al., 2015, Lim et al., 2015). However, some studies have found that such enlargements are evident in ASD individuals only at an early age, with no abnormalities observed in their older counterparts (Courchesne et al., 2001a, Aylward et al., 2002). Moreover, a meta-analysis of 277 ASD individuals found evidence for increased GMV in the insula and parietal regions in pre-adolescent ASD children, while adults with ASD showed decreased GMV in these regions compared to typically developing individuals (Nickl-Jockschat et al., 2012).

Another approach to MRI analysis is known as region of interest (ROI) analysis. In this approach, the search area within the brain is limited to one or more pre-specified

areas or brain regions, usually based on *a priori* hypotheses, reducing the number of comparisons being made and thus increasing the statistical power to detect group differences (Poldrack, 2007). This approach is useful if there is a strong justification for investigating the ROI, but is also a less statistically stringent method compared to whole-brain analysis. One ROI investigation of structural abnormalities in the DLPFC in children and adolescents with ASD found increased GMV in this region in ASD children compared to typically-developing children and showed that this was related to increased symptom severity as indexed by the ADOS (Mitchell et al., 2009). Despite these findings, decreases in frontal GMV have also been observed in children and adolescents with ASD compared to controls in orbitofrontal cortex (OFC), mPFC, right IFC and DLPFC (Zilbovicius et al., 1995, Kwon et al., 2004, McAlonan et al., 2005, McAlonan et al., 2008, Mengotti et al., 2011, Riva et al., 2011).

In addition to cortical regions, structural abnormalities in the cerebellum have been consistently implicated in the pathophysiology of ASD, particularly in adolescence (DeRamus and Kana, 2015), particularly during attention functions (Courchesne et al., 1994, Allen and Courchesne, 2003). The cerebellar vermis (lobules VI-VII) was among the first regions to be shown as abnormally small in ASD patients using MRI (Courchesne et al., 1988), and since this early study, many studies have replicated this finding, predominantly in the left cerebellar hemisphere and vermis (Courchesne et al., 1988, Courchesne et al., 1994, Hashimoto et al., 1995, Courchesne, 1997, Carper and Courchesne, 2000, Courchesne et al., 2001a, Courchesne et al., 2007, Cauda et al., 2011, Nickl-Jockschat et al., 2012, Riva et al., 2013, DeRamus and Kana, 2015, Foster et al., 2015), while others have been unable to find such differences (Hashimoto et al., 1992, Holttum et al., 1992, Piven et al., 1992). Moreover, reduced cerebellar volumes have been linked to increases in frontal grey matter of ASD individuals (Carper and Courchesne, 2000) as well as ASD symptomatology in children (Riva et al., 2013),

suggesting a role for fronto-cerebellar networks in the pathophysiology of ASD. Given age-related findings of volumetric changes in autism (Nickl-Jockschat et al., 2012), it is possible that these discrepancies stem from heterogeneity among different subgroups of ASD patients as well as variation across age groups (Courchesne et al., 1994). With specific regard to child and adolescent studies, increased (Sparks et al., 2002, Palmen et al., 2005a, Bonilha et al., 2008) as well as decreased (Courchesne et al., 2001a, Brun et al., 2009, Webb et al., 2009, Foster et al., 2015) total cerebellar volumes and grey and white matter cerebellar volumes have been found, highlighting the need for further research into abnormalities associated with ASD during specific developmental stages across the lifespan.

Structural abnormalities in the temporal and parietal lobes in ASD have also been investigated. Despite the implication of the temporo-parietal junction in social cognition and mentalising, and its relevance to ASD (Lombardo et al., 2011), structural findings in the temporal lobe in ASD are mixed. In addition to increased total temporal lobe volumes (Waiter et al., 2004, Brun et al., 2009, Jou et al., 2010), increased (Abell et al., 1999, Waiter et al., 2004, Bonilha et al., 2008, Mengotti et al., 2011, Xiao et al., 2014, Foster et al., 2015, Lim et al., 2015) and decreased GMV (Boddaert et al., 2004, Kwon et al., 2004, Brieber et al., 2007, McAlonan et al., 2008, Riva et al., 2011, Foster et al., 2015) and decreased white matter volumes (Waiter et al., 2005, Bonilha et al., 2008) have been observed in children and adolescents with ASD compared to typically-developing controls of the same age. The parietal lobe has been implicated in sensory processing and integration (Blakemore and Sirigu, 2003). However, limited findings from paediatric ASD sMRI studies of parietal abnormalities are mixed, with one small study finding increased grey matter and decreased white matter volume in the parietal lobe of ASD adolescents relative to controls (Bonilha et al., 2008). Another larger study with 20 ASD individuals finding increased GMV in inferior and superior parietal

regions (Mengotti et al., 2011), whereas a study of 17 medication-naïve ASD adolescents found decreased parietal lobe grey matter compared to controls (McAlonan et al., 2005) and another study of 21 patients found decreased grey matter in the right inferior parietal lobe in ASD individuals compared to controls (Riva et al., 2011).

Subcortical structural abnormalities have also been found in children and adolescents with ASD; the thalamus and basal ganglia (BG) have been implicated in repetitive behaviours (Hollander et al., 2005, Langen et al., 2011, Wolff et al., 2013, Langen et al., 2014) and inhibition (Dambacher et al., 2014). Whole-brain studies in ASD have found decreased grey matter in the caudate, nucleus accumbens and globus pallidus in children with ASD relative to controls (McAlonan et al., 2005, McAlonan et al., 2008, Riva et al., 2011). An ROI study found that increased right caudate and total putamen volumes in individuals with ASD correlated positively with repetitive behaviour scores on the ADI, particularly with higher order OCD-like repetitive behaviours (Hollander et al., 2005). Moreover, the thalamus is closely interconnected with the BG (Alexander and Crutcher, 1990), and whole brain analyses have found decreased GMV in the thalamus in children with ASD relative to controls (Waiter et al., 2004), supported by an ROI study (Tamura et al., 2010). Nonetheless, other studies have shown increased GMV in the thalamus, putamen and caudate (Bonilha et al., 2008, Foster et al., 2015). A longitudinal ROI study of striatal volumes and growth rates found that while there were no differences in GMV of the striatum between ASD individuals and controls at either time point, ASD individuals had increased growth rates of the caudate in early childhood relative to controls which was related to rigid behaviours later in childhood (Langen et al., 2014).

The medial temporal lobe comprises a group of subcortical structures often referred to as the limbic system. These structures include the amygdala, hippocampus,

hypothalamus and parahippocampal gyrus and have been associated with the pathophysiology of autism, specifically with regard to social function; the amygdala in particular has been implicated in social cognition (Brothers, 2002) because of its relevance to emotion processing and anxiety (LeDoux, 2000) and was first linked to autism by Kemper and Bauman (Kemper and Bauman, 1993) in post-mortem studies. More recently, MRI evidence of amygdala abnormalities in ASD led Baron-Cohen et al. to link this structure to the social impairments commonly observed in ASD (Baron-Cohen et al., 2000), a theory that has since been supported by more recent sMRI investigations in childhood (Munson et al., 2006, Mitchell et al., 2009, Schumann et al., 2009). Paediatric sMRI studies have found increased total amygdala volumes and faster growth rates in young children with ASD relative to controls (Sparks et al., 2002, Schumann et al., 2004, Schumann et al., 2009, Nordahl et al., 2012), and an ROI study in 42 children with ASD found that increased total volumes and right (but not left) amygdala volumes were associated with parent-reported anxiety symptoms (Juranek et al., 2006), linking the role of this region in anxiety to autism. Other sMRI findings of limbic structure abnormalities in children and adolescents with ASD include increased GMV in the parahippocampal gyrus (Waiter et al., 2004, Bonilha et al., 2008). Moreover, Schumann and colleagues found that while amygdala volumes were increased in young toddlers but not adolescents with ASD relative to controls, increased hippocampal volumes were evident in ASD across development from early childhood into adolescence (Schumann et al., 2004). However, there have also been some studies reporting decreased GMV in the hippocampus-amygdala complex (Brieber et al., 2007), parahippocampal gyrus (Ke et al., 2008) and hypothalamus (Kurth et al., 2011).

The above findings of structural abnormalities in children and adolescents with ASD suggest important conclusions but also highlight the heterogeneity within the ASD literature and the need for further work focussing on more refined groups of ASD

individuals and larger sample sizes to account for differences in age, sex, symptom severity and subtype. Nonetheless, findings of increased total cerebral, DLPFC and amygdala volumes have been widely replicated in child and adolescent samples (Sparks et al., 2002, Schumann et al., 2004, Waiter et al., 2004, Carper and Courchesne, 2005, Palmen et al., 2005b, Hazlett et al., 2006, Brun et al., 2009, Mitchell et al., 2009, Schumann et al., 2009, Stigler et al., 2011, Nordahl et al., 2012, Foster et al., 2015), supporting the theory of early brain overgrowth in children with ASD relative to age-matched peers (Courchesne et al., 2001a, Courchesne, 2004). Although findings of decreased cerebellar volumes are relatively congruent (Courchesne et al., 1988, Courchesne et al., 1994, Hashimoto et al., 1995, Courchesne, 1997, Carper and Courchesne, 2000, Courchesne et al., 2001a, Courchesne et al., 2007, Cauda et al., 2011, Nickl-Jockschat et al., 2012, Riva et al., 2013, DeRamus and Kana, 2015, Foster et al., 2015), there exist inconsistencies in the literature for structural findings in the cerebellum, temporal and parietal lobes, again highlighting a need for further investigation in large samples to more precisely determine regions of increased and/or decreased grey matter in ASD groups relative to the typically developing population. Nonetheless, abnormalities within fronto-limbic networks including the amygdala have been associated with social communication deficits, and structural abnormalities in these regions as well as the BG and cerebellum have been linked to ASD symptomatology, including repetitive behaviours and social impairments (Riva et al., 2013, Langen et al., 2014, Richter et al., 2015, Yang et al., 2016). These abnormalities are identifiable from an early age, possibly suggesting early-life biomarkers that may be indicative of the development of autistic symptoms later in development. This yields clinical implication, providing a potential avenue into further research for early identification and possible treatment of ASD-related behaviours.

2.2.2 Brain structure abnormalities in OCD

Early anatomical studies in primates were the first to document specialized brain circuits connecting the BG to the frontal cortex, termed 'fronto-striatal loops' (Alexander et al., 1986), which work in parallel but have specific functions based on their connections to varying regions of the frontal lobe. Among these fronto-striatal loops is the orbito-frontal cortico-striato-thalamo-cortical loop, connecting the OFC to the caudate head and ventral striatum, continuing to the medio-dorsal thalamus and returning to the OFC. This pathway has since been modified to include limbic structures including the basolateral amygdala and hippocampus as well as the ACC, suggesting a role for this circuitry in affective states, inhibitory control and emotion cognition (Lawrence et al., 1998, Phillips et al., 2003). As such, neuroimaging research in OCD has long focused on these orbitofronto-striatal loops (McGuire et al., 1994, Saxena et al., 1998b, Graybiel, 2000, Saxena et al., 2001, Mataix-Cols and van den Heuvel, 2006). Early PET (Baxter et al., 1987, Mazziotta et al., 1988) and lesion studies (Laplane et al., 1989, Chacko et al., 2000, Carmin et al., 2002, Kim and Lee, 2002, Ogai et al., 2005) primarily implicated the OFC and BG in the pathophysiology of OCD, leading many researchers to focus on structural differences within these affective fronto-striatal loops in ROI studies (for reviews, see (Maia et al., 2008, Menzies et al., 2008)). These investigations initially provided relatively robust evidence for reduced OFC volumes in OCD patients, as well as evidence for BG abnormalities, although findings for the direction of BG abnormalities was less consistent, possibly due to heterogeneity of OCD patients included in these studies.

This work led to the development of influential 'fronto-striatal' models of OCD, initially posited by Saxena and colleagues and since elaborated upon by many others. These models have been termed many things but mostly centre around the involvement

of the OFC, ACC and caudate nucleus and their interconnections via cortico-striato-thalamo-cortical (CSTC) affective and cognitive loops (Baxter Jr et al., 1996, Saxena et al., 1998a, Graybiel, 2000, Saxena and Rauch, 2000, Lichter and Cummings, 2001, Maia et al., 2008). It has been proposed that OCD results from an imbalance between "direct" excitatory and "indirect" inhibitory OFC/ACC CTSC pathways through the BG (Alexander et al., 1986, Albin et al., 1989, DeLong, 1990), such that excessive activity in direct pathways results in a positive feedback loop and 'traps' patients in a cycle of obsessive thoughts (Graybiel, 2000, Saxena and Rauch, 2000, Baxter et al., 2001, Saxena et al., 2001) (Figure 2.1).

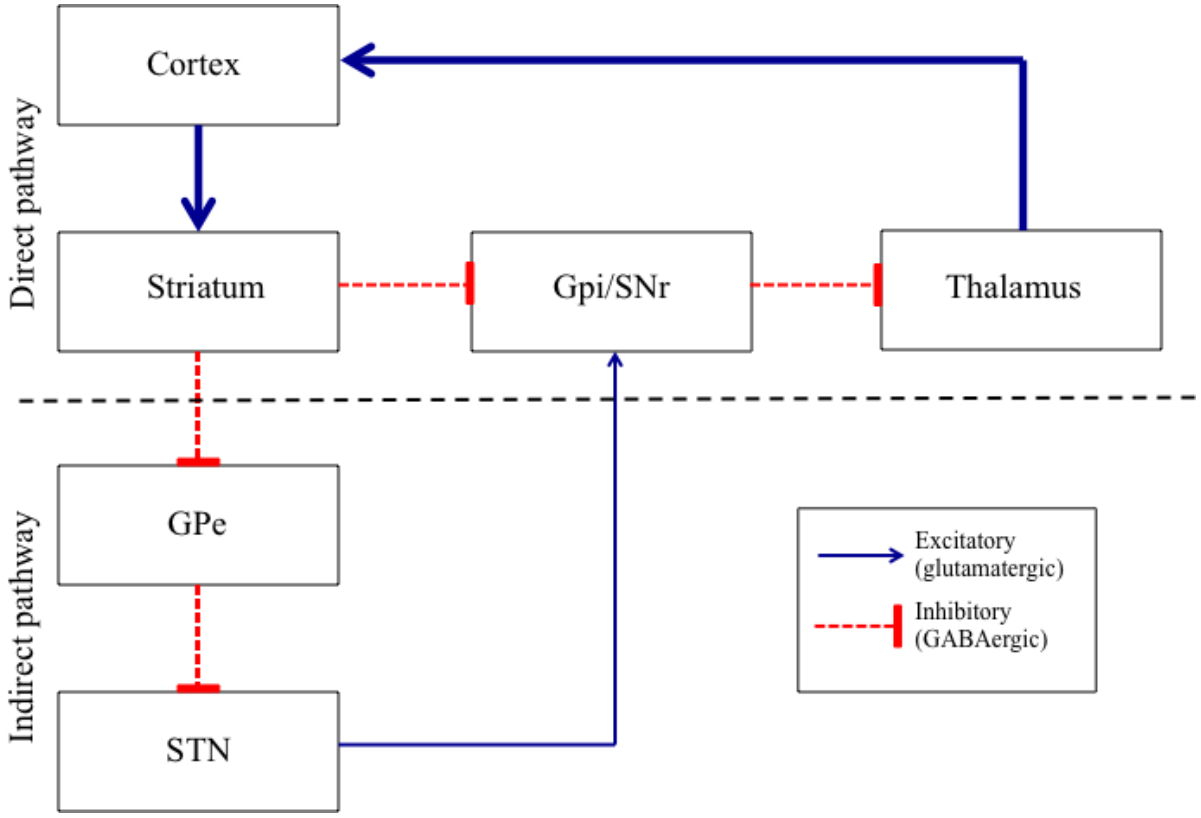


Figure 2.1 Schematic conceptualization of cortico-striato-thalamo-cortical loops

Adapted from Maia et al., 2008 and Menzies et al., 2008. The direct pathway runs from the cortex to the striatum via excitatory glutamatergic (blue arrows) and inhibitory GABAergic connections (red dashes). It then runs directly to the internal segment of the globus pallidus (GPi) and substantia nigra pars reticulata (SNr), then to the thalamus and returns to the cortex. The indirect pathway runs from the cortex to the striatum, then to the external segment of the globus pallidus (GPe), then to the subthalamic nucleus (STN), then to the Gpi/SNr, thalamus, and finally back to the cortex. As the direct pathway contains an even number of inhibitory connections, its net effect from cortex back to cortex is excitatory, whereas the indirect pathway has an odd number of inhibitory connections, so the net effect is inhibitory. Saxena (1998) and others (e.g. Graybiel & Rauch, 2000) proposed that OCD occurs as a result of an imbalance between these two pathways, with excessive activity in direct pathways.

However, while models of orbitofronto-striatal dysregulation have received much subsequent focus in the OCD literature, the plausibility and specificity of these models has also been called into question. Recent reviews and meta-analyses of grey and white matter alterations in OCD have suggested that other brain regions such as the parietal lobe may also be implicated in OCD (Menzies et al., 2008, Radua and Mataix-Cols, 2009, Radua et al., 2010). Moreover, in addition to hyperactivity within affective OFC/ACC medial prefrontal limbic circuitry, neurocognitive reviews of OCD have also

implicated reduced activation in dorsal fronto-parietal-striatal cognitive networks (Menzies et al., 2008).

Before reviewing the sMRI literature in OCD, it is important to note that among OCD studies, it is quite common for some or all of the patients to be receiving antidepressant or neuroleptic medication at the time of testing or have a history of medication use (e.g. 4-week washout before testing). The long-term effects of these medications are relatively unknown, but there is evidence for the effects of serotonin on the brain (Murphy et al., 2008, Murphy, 2010), and thus results should be interpreted with this caveat in mind. Moreover, co-morbid depression and anxiety is common in OCD, and the effects of these comorbidities are often not accounted or controlled for in OCD studies. Additionally, most OCD investigations include patients with a range of symptom profiles, but it has been shown that different symptom profiles of OCD can have different underlying neural correlates (Phillips et al., 2000, Mataix-Cols et al., 2004).

In line with orbitofrontal-striatal models, much of the evidence for frontal lobe structural abnormalities in OCD implicates the OFC and comes from ROI studies, primarily in adults, which have found reduced GMV bilaterally in this region in patients relative to controls (Szeszko et al., 1999, Choi et al., 2004, Atmaca et al., 2006, Atmaca et al., 2007) (one study (Kang et al., 2004) found reductions only in the left OFC). Evidence of reduced OFC volume in OCD has also been supported by whole-brain studies (Pujol et al., 2004, van den Heuvel et al., 2009, Togao et al., 2010, Hou et al., 2013). However, there have also been studies finding increased OFC volumes in adults and adolescents relative to controls (Kim et al., 2001, Valente Jr et al., 2005, Christian et al., 2008, Szeszko et al., 2008, Britton et al., 2010). Notably, findings in adolescence were limited to analyses excluding patients with comorbid depression (Christian et al.,

2008). Indeed volumetric abnormalities in this region in OCD seem to be linked to the presence or absence of comorbid depression (Piras et al., 2015). In another adolescent study, increased GMV in left medial OFC was related to greater symptom severity (Szeszko et al., 2008). Despite the implications of the OFC in OCD, a meta-analysis including 12 studies of 401 adults with OCD found GMV reductions in patients relative to controls in dmPFC and ACC but critically did not find group difference in the OFC (Radua and Mataix-Cols, 2009). There have been only 8 published studies of whole-brain voxel-based morphometry (VBM) of structural abnormalities in paediatric OCD, similarly producing somewhat mixed results of frontal abnormalities. Some studies (Carmona et al., 2007, Gilbert et al., 2008a) showed smaller GMV in middle frontal cortex and ACC while other studies (Szeszko et al., 2008, Britton et al., 2010, Zarei et al., 2011) found enhanced volumes in putamen, ACC, IFC and OFC in patients relative to controls. This heterogeneity in findings is supported by a systematic review of the paediatric OCD VBM literature (Ahmed et al., 2012) which concluded that children with OCD have reduced GMV in the ACC that is consistent with similar findings in adult studies (Ahmed et al., 2012). The largest VBM study of paediatric OCD similarly found absolute reductions compared to controls in medial frontal gyrus and ACC (Pujol et al., 2004). Other studies have found reduced GMV in regions involved in conflict monitoring and cognitive control (Bush et al., 2000) including left caudal and dorsal ACC in adults (Matsumoto et al., 2010) and adolescents (Carmona et al., 2007, Gilbert et al., 2008a). In other studies (including a meta-analysis; (Norman et al., 2016)) incorporating adults and children with OCD, findings in the dorsal ACC extend into nearby regions of the medial frontal wall (Valente Jr et al., 2005, Kopřivová et al., 2009, Norman et al., 2016), an area commonly associated with stimulus representation (Rushworth et al., 2007). Thus, while mixed results are likely a result of the vast heterogeneity in samples (adults vs. children), methods (ROI vs. whole-brain) and

clinical status (medication, symptom severity), this evidence largely supports initial findings of reduced medial prefrontal, orbitofrontal and ACC GMV in individuals with OCD, supporting orbitofronto-striatal models.

The BG is another region critically involved in CSTC models, as whole-brain meta-analyses (Radua and Mataix-Cols, 2009, Radua et al., 2014a, Norman et al., 2016) have shown that the BG, encompassing the striatum and thalamus, is increased in volume in both adults and children with OCD compared to controls. However, some smaller ROI studies in adults (Kang et al., 2004, Atmaca et al., 2006, Atmaca et al., 2007) and medication-naïve children (Szeszko et al., 2004) report no differences between patients and controls, particularly in the caudate. It has also been shown that volumetric changes in the putamen and nucleus accumbens are particularly insensitive to age in OCD such that volumes in this region are preserved with ageing in OCD but decline with age in healthy populations, as demonstrated in a large cross-sectional study (Pujol et al., 2004) and confirmed by a recent cross-sectional mega-analysis (deWit et al., 2014). Moreover, the largest and most recent meta- and mega-analysis to date (ENIGMA consortium; (Boedhoe et al., 2017)) used an ROI approach examining subcortical volumes and found that in the meta-analysis (35 datasets), adults with OCD had larger pallidum GMV compared to controls, but no differences in any of the investigated ROIs were observed between children with OCD and control children. Moreover, the mega-analysis (1,495 OCD adults, 335 OCD children) found that children, but not adults, with OCD had larger thalamus GMV compared to healthy controls (which was moreover pronounced in patients without comorbid anxiety) (Boedhoe et al., 2017). This may partially explain heterogeneity among the literature in striatal and BG volumetric findings, as age is likely an influential factor in GMV of these regions; a smaller study (Hoexter et al., 2013) found that enhanced caudate and putamen volumes seen in OCD may be dependent on age or treatment status.

Interestingly, a systematic review reported that age significantly contributed to striatal enlargement, extending the above mega-analysis findings and suggesting that volume increases in these regions across the lifespan in OCD (Piras et al., 2015). Furthermore, paediatric (Szeszko et al., 2008) and adolescent (Zarei et al., 2011) studies as well as meta-analyses of adult studies (Radua and Mataix-Cols, 2009) and combined adolescent and adult studies (Rotge et al., 2009, Peng et al., 2012) have found that increased bilateral putamen volumes and effect sizes for left and right thalamus increases are associated with symptom severity in medicated as well as medication-naïve OCD samples, linking volumetric increases in this region to the clinical expression of OCD. Enhanced thalamus volume has also been found in OCD patients relative to controls (Kim et al., 2001, Christian et al., 2008, Yoo et al., 2008), and this enlargement was concurrent with OFC enlargement in two of these studies (Kim et al., 2001, Christian et al., 2008), providing additional support for CTSC network abnormalities in OCD. It has been suggested that intra-study variability in caudate and BG volumes in OCD may be a result of variability in the CTSC loops that run via the BG (Maia et al., 2008); different parts of the BG (e.g. ventral striatum versus caudate head) comprise different loops, and it may be that alterations in a subcomponent of the BG do not influence the overall volume of this region.

Studies of structural abnormalities in OCD do not widely implicate the cerebellum, but recent work suggests that perhaps more attention should be given to this region when discussing models of OCD (deWit et al., 2014). Findings of cerebellar abnormalities have been mixed; several studies (Pujol et al., 2004, Rotge et al., 2010) including a meta-analysis of 15 studies (Peng et al., 2012) and another of 30 studies (Norman et al., 2016), as well as a large-scale mega-analysis of 412 individuals with OCD which included paediatric patients (deWit et al., 2014), found that compared to controls, adult and paediatric patients with OCD had increased cerebellar volumes,

while another study found reduced left cerebellar volumes in patients relative to controls (Kim et al., 2001), and a meta-analysis found no volumetric differences in this region in patients relative to controls (Radua and Mataix-Cols, 2009). Moreover, bilateral cerebellar volumes have been found to be inversely correlated with Y-BOCS scores in adults, suggesting that smaller cerebellar volumes in OCD are associated with greater symptom severity (van den Heuvel et al., 2009), but the opposite association has been observed in adolescents (Zarei et al., 2011). Again, it is probable that these conflicting findings are due to heterogeneous samples, comorbidity, and medication use, but this suggests that more consideration of the cerebellum in the pathophysiology of OCD may be warranted, with particular attention given to developmental effects.

In the medial temporal and limbic lobes, studies in both children and adults generally report enlarged volumes in a paralimbic network of the medial temporal lobe, amygdala, hippocampus, parahippocampus and hypothalamus in OCD patients relative to controls (Kim et al., 2001, Valente Jr et al., 2005, Yoo et al., 2008, Lázaro et al., 2009, Hou et al., 2013, Tang et al., 2015). However, one ROI study in adults with OCD reported reduced bilateral hippocampal but enlarged left amygdala volumes in patients relative to controls (Kwon et al., 2003). Moreover, one of these studies (Valente Jr et al., 2005) found that volumes in the parahippocampal gyrus and bilateral amygdala were negatively associated with duration of treatment. However, a longitudinal study in children and adolescents (Lázaro et al., 2009) found that increased GMV in the right temporal pole extending into parahippocampal gyrus, hippocampus and amygdala was only evident in post- but not pre-treatment scans and only at a relatively liberal threshold of $p<0.001$ uncorrected. Specific to the insula, results are slightly more conflicting. Some adult studies (Kim et al., 2001, Valente Jr et al., 2005) report increased volumes in patients relative to controls in the right (Kim et al., 2001) and left (Valente Jr et al., 2005) insula, while other studies (Pujol et al., 2004, Yoo et al., 2008)

report reduced volumes in this region. However, this heterogeneity could be due to lack of distinction between anterior and posterior insular cortices, supported by evidence from an ROI study specifically investigating anterior/posterior divisions in the insula in a large sample of adults with OCD which found enlarged anterior but reduced posterior insula volumes (Song et al., 2011).

Temporal and parietal regions are less consistently reported to be abnormal in OCD compared to the literature in ASD, but differences have been observed. A study investigating GMV in a sample of adults with OCD found that patients had enhanced GMV relative to controls in left superior and right middle temporal gyri and left inferior parietal lobe (Kim et al., 2001), and a later study extended these findings to a group of medication-naïve children, showing enhanced right superior temporal and bilateral parietal volumes in patients relative to controls (Szeszko et al., 2008). A more recent meta-analysis encompassing 30 studies comparing 938 children and adults with OCD to 942 controls found that OCD patients had decreased GMV relative to controls in a large left-hemispheric cluster encompassing the superior temporal lobe (Norman et al., 2016), and enhanced GMV in right superior parietal lobe in OCD has been negatively associated with comorbid depression (Radua and Mataix-Cols, 2009). In line with this evidence, some reports suggest that the parietal cortex may play a bigger role in OCD than previously thought (Menzies et al., 2007, Menzies et al., 2008, van den Heuvel et al., 2009). Moreover, van den Heuvel et al. (van den Heuvel et al., 2009) found that GMV (and white matter volumes) in the temporal lobe were differentially associated with different symptom dimensions in OCD; bilateral temporal volumes were negatively associated with harm/checking symptoms, while they were positively associated with symmetry/ordering symptoms. These results, while limited, suggest that in addition to fronto-striatal regions, temporo-parietal regions may also play a role in the pathophysiology of OCD and presentation of OCD-related symptoms.

2.3 Summary of brain structure abnormalities in ASD and OCD

Based on the findings outlined above, there seem to be both similarities and potential differences in brain structure abnormalities between ASD and OCD, notably in dorsolateral and medial orbitofronto-striatal regions, with enhanced dorsal lateral and medial frontal volumes observed in ASD but reduced medial and OFC volumes observed in OCD (although there is vast heterogeneity in the literature concerning both groups). No studies have directly compared brain structure between these disorders, but drawing upon the existing literature in each disorder, including reviews, mega- and meta-analyses, can lead to hypotheses about similarities and differences.

Regarding mostly cross-sectionally derived hypotheses about developmental trajectories of brain structure in each disorder, ASD is often characterised by the seminal finding of early brain overgrowth in childhood followed by delayed growth or even decreased volumes in patients with ASD relative to typically-developing children (Courchesne et al., 2001b). A neurodevelopmental account of OCD is less consistent, but studies have hinted at the implications of age and neurodevelopment in the emergence of OCD-related symptoms (Rosenberg and Keshavan, 1998, Menzies et al., 2008). Structural imaging studies in OCD more commonly include adult patients and often do not account for factors such as age which could plausibly have an effect on brain structure differences between children and adults with OCD. More recently, large-scale cross-sectional studies in OCD have found age-related changes in brain structures related to CSTC models of OCD including putamen and OFC, with studies suggesting that striatal volumes may be preserved across the lifespan in OCD (deWit et al., 2014), and others suggesting that volumetric differences are evident between adults, but not children, with OCD and controls (Boedhoe et al., 2017). However, studies of the developmental trajectory of OCD in early childhood are lacking, as OCD-related

symptomatology usually emerges later in development, and there are no longitudinal studies to date following individuals with OCD across the lifespan (Ruscio et al., 2010).

There appears to be an increase in total cerebral, dorsolateral and medial prefrontal, and striatal grey matter volumes in children with ASD relative to typically developing children (Sparks et al., 2002, Waiter et al., 2004, Carper and Courchesne, 2005, Hazlett et al., 2006, Bonilha et al., 2008, Brun et al., 2009, Mitchell et al., 2009, Hyde et al., 2010, Stigler et al., 2011, Foster et al., 2015, Lim et al., 2015) (although decreased mPFC volumes have also been observed (Zilbovicius et al., 1995, Kwon et al., 2004, McAlonan et al., 2005, McAlonan et al., 2008, Mengotti et al., 2011, Riva et al., 2011), highlighting the heterogeneity among individuals included in ASD studies). On the other hand, reduced medial and orbitofrontal volumes are consistently reported in children with OCD relative to healthy controls (Ahmed et al., 2012, Norman et al., 2016), and OCD has been associated with abnormal BG and striatal volumes, the direction of which may be age-dependent (e.g. reduced or no difference in children with OCD but enhanced in adult patients relative to controls) (Toga et al., 2006, Piras et al., 2015). Although the direction of these abnormalities has been less consistently demonstrated, it seems that there is a trend in the literature among reviews and meta-analyses towards increased thalamic and striatal volumes in individuals with OCD, which would be in line with theories of a functional dysregulation within medial prefrontal and orbitofronto-striatal networks where BG are overactive and larger in volume and poorly controlled by prefrontal regions that are reduced in volume and function (Menzies et al., 2008, Norman et al., 2016).

It is speculative to link structural alterations to observed behaviour, but a better understanding of structural abnormalities that are either shared or disorder-specific in ASD and OCD is a critical first step toward identifying biologically-based markers of

these disorders and accompanying symptoms. However, no studies have compared these two disorders on the basis of structural brain differences that may be important underlying factors in cognitive deficits observed in each disorder. Preliminary conclusions regarding similarities and differences can be made based on the above evidence. Children with ASD have been associated with early brain overgrowth resulting in increased volumes in medial and lateral fronto-striatal, fronto-limbic and fronto-temporal structures (Courchesne, 2004, Nordahl et al., 2012, Lange et al., 2015), which later in life appear to be diminished relative to controls, while orbitofrontal structures involved in CSTC loops are more consistently implicated in OCD, with a focus in the literature on models of orbitofronto-striatal dysregulation (reduced OFC volumes but enhanced BG volumes) (McGuire et al., 1994, Saxena et al., 1998b, Graybiel, 2000, Saxena et al., 2001, Mataix-Cols and van den Heuvel, 2006, Menzies et al., 2008). This PhD aimed to test this hypothesis by conducting a comparative meta-analysis of all whole-brain structural VBM studies in the two disorders. Thus, a direct comparison of structural differences between these disorders is presented in Chapter 4 via comparative meta-analysis of whole-brain VBM studies.

CHAPTER 3 - FUNCTIONAL MRI ABNORMALITIES IN ASD AND OCD

3.1 Introduction

fMRI enables the investigation of brain activation while a subject performs a cognitive task in an MRI scanner (Poldrack et al., 2011). This method is based on the concept that when a certain part of the brain is active (e.g. being used for a particular task/function), regional blood flow to this area is increased, delivering excess glucose and oxygen to the neurons of that region. This results in 'active' brain regions having more oxygenated blood at a given time than regions which are less active during that task, a mechanism known as the Blood-Oxygen Level Dependent (BOLD) response (Ogawa et al., 1990). The BOLD response is integral to the theory behind fMRI, exploiting the magnetic properties of oxy- and deoxyhaemoglobin in the blood. Deoxyhaemoglobin is a paramagnetic molecule, meaning that it causes a disturbance in the scanner's magnetic field, which in turn affects the magnetic resonance of the protons in the water molecules of the blood surrounding the deoxyhaemoglobin, an effect that can be measured by the scanner (Turner et al., 1998).

fMRI (and sMRI) are advantageous over other methods of brain imaging such as electroencephalography (EEG) because of their superior spatial resolution, and fMRI is a preferred method for investigating brain function in child, adolescent and clinical populations, as it is far less invasive compared to Single-Photon Emission Computed Tomography (SPECT) or Positron Emission Tomography (PET), which use injected radioactive isotopes. Given that the focus of this PhD is cognitive control, attention, and reward-based decision-making in adolescents with ASD and OCD, the paediatric and adolescent fMRI literature in these domains will be reviewed below, and adult studies will be discussed when there is a dearth of developmental work. The fMRI literature of other cognitive functions will also be discussed briefly.

3.2 Cognitive control and inhibition

3.2.1 fMRI studies of cognitive control in ASD

There have been five fMRI studies of inhibitory control in children/adolescents with ASD, two investigating motor inhibition (Ambrosino et al., 2014, Chantiluke et al., 2015b) and three examining cognitive interference inhibition (Solomon et al., 2009, Vaidya et al., 2011, Solomon et al., 2014). A table of all whole-brain fMRI studies of inhibitory control in ASD (as well as OCD), along with their findings, is presented in Chapter 4. During whole-brain and ROI studies of cognitive interference inhibition, adolescents with ASD have shown decreased activation in bilateral middle/superior frontal cortex including DLPFC and ACC, superior parietal lobe and precuneus, and in left IPL and premotor cortex and right caudate relative to controls, with worse task performance (more errors) compared to controls (Solomon et al., 2009, Vaidya et al., 2011, Solomon et al., 2014). Moreover, Solomon et al. (Solomon et al., 2014) found reduced sensorimotor and parietal activation in older vs. younger adolescents with ASD. During motor inhibition, one study showed that children with ASD had increased activation in bilateral IFG and but decreased left IPL activation (Chantiluke et al., 2015b), while an earlier study (Ambrosino et al., 2014) showed no differences between ASD individuals and controls. Across age groups, it has broadly been observed that during successful motor response and interference inhibition, both children and adults with ASD show decreased ACC, right IFC, bilateral superior/middle frontal cortical and premotor activation (Kana et al., 2007, Solomon et al., 2009). Moreover, increased left IFC and OFC activation have been observed in adults with high-functioning ASD (Schmitz et al., 2006), but there is significant heterogeneity in the adult literature, with other response inhibition studies (e.g. (Daly et al., 2014, Shafritz et al., 2015)) showing decreased IFC/VLPFC activation in ASD adults. This discrepancy can partially be

attributed to task differences, small sample sizes, and sample/age heterogeneity but highlights the need for additional studies. A table of all whole-brain fMRI studies of inhibitory control in ASD, along with their findings, is presented in Chapter 4, which also presents a comparative meta-analysis of inhibitory control functions in ASD and OCD.

fMRI studies of switching in adults with ASD have found abnormal activation in fronto-striatal, parietal and cerebellar attention networks in ASD relative to typically-developing individuals (Schmitz et al., 2006, Shafritz et al., 2008). In a target detection set-shifting task requiring flexible attention, ASD individuals exhibited activation to target stimuli in ACC and IPS that decreased as a function of RRBI severity (Shafritz et al., 2008). Schmitz et al. (Schmitz et al., 2006) also used a set-shifting task and found that ASD individuals had increased activation in left frontal and insular regions and right inferior and left mesial parietal lobes during switch trials. Schmitz and colleagues also inlcuded a Go/No-go task and found that ASD individuals had increased left inferior and orbitofrontal activation during response inhibition (Schmitz et al., 2006).

3.2.2 fMRI studies of cognitive control in OCD

As it has been argued that symptoms of OCD may arise from a failure to inhibit certain thoughts or behaviours (van Velzen et al., 2014), inhibitory control is a potentially useful construct for studying the underlying neural mechanisms implicated in the pathophysiology of OCD (Nakao et al., 2005, Woolley et al., 2008, Page et al., 2009, Morein-Zamir et al., 2015, Norman et al., 2016). The ACC has been commonly implicated in cognitive interference inhibition in OCD in both children and adult studies, but results are not consistent. Some studies in adults (Fitzgerald et al., 2005) and children (Huyser et al., 2011) with OCD have shown ACC hyperactivation in patients relative to controls, while others (Nakao et al., 2005, Rubia et al., 2011) have

shown decreased activation. However, findings of hyperactivation are possibly due to the ACC's involvement in conflict processing and error monitoring, as a recent meta-analysis of 14 studies of inhibitory control across multiple inhibition tasks found decreased ACC activation in OCD (Norman et al., 2016). Moreover, increased activation in fronto-striatal regions including IFG and putamen as well as increased functional connectivity between the putamen and fronto-striatal and parietal regions has also been observed in adult OCD patients relative to controls during a Simon flanker task (Marsh et al., 2014). During motor inhibition tasks, decreased activation in inferior and orbitofronto-striato-thalamo-cortical regions has been found in adults (Roth et al., 2007, Page et al., 2009, Kang et al., 2013) and children (Woolley et al., 2008, Rubia et al., 2010a), although one ROI study found increased activation in these regions, namely in lateral OFC, caudate and thalamus (Maltby et al., 2005). The most consistent finding among these studies is decreased activation in DLPFC, IFG, striatum and thalamus in individuals with OCD (Roth et al., 2007, Woolley et al., 2008, Page et al., 2009, Rubia et al., 2010a, de Wit et al., 2012). It should also be noted, however, that two fMRI studies investigating cognitive interference inhibition in children found no activation differences between patients and controls (Fitzgerald et al., 2010, Huyser et al., 2011), suggesting that perhaps there is a developmental effect of abnormal response inhibition in OCD, although more studies are needed to confirm this hypothesis.

Several adult and paediatric studies (Gu et al., 2008, Woolley et al., 2008, Page et al., 2009, Britton et al., 2010, Rubia et al., 2010a, Han et al., 2011) have investigated cognitive flexibility and switching in OCD. Many of these studies were in relatively small (N=10) samples of mostly medicated patients but suggest cognitive control difficulties in adolescent OCD. Findings of reduced left frontocortical activation are supported by another study in medicated but still symptomatic OCD adolescents (Britton et al., 2010). This study examined cognitive flexibility using a set-shifting

paradigm and found similar results, showing reduced activation in left IFG that was negatively correlated with behavioural shift costs (the reaction time difference between mixed versus repeated trials) in OCD adolescents. Britton and colleagues posited that this abnormality in fronto-striatal regions could be related to immaturity in attentional systems in OCD, as OCD individuals lag in the developmental shift from reliance on fronto-parietal systems to fronto-striatal systems for set-shifting (Sohn et al., 2000). Another paediatric study investigating visuo-spatial attention during cognitive flexibility in OCD relative to ADHD found that adolescent boys with OCD did not differ from control participants (except at a trend-level in mPFC) on brain activation during set-shifting (Rubia et al., 2010a). However, this study also employed an inhibitory control task measuring attention allocation (stop task) and found that boys with OCD and boys with ADHD, the cardinal disorder of inattention, exhibited shared medial prefrontal underactivation relative to controls during failed inhibition (Rubia et al., 2010a). Moreover, an earlier fMRI study of inhibitory control showed temporo-parietal underactivation in boys with OCD (Woolley et al., 2008). Another investigation of task-switching in adults with OCD found that compared to controls, patients had widespread reduced activation during switching in bilateral VLPFC, DLPFC, caudate, hippocampus and parietal lobe, and in right rostral ACC, OFC and insula and left dorsal ACC, which furthermore was up-regulated with pharmacotherapy (although drug therapy/doses were not standardised across patients) (Han et al., 2011). In a study of un-medicated adults with OCD during cognitive flexibility, patients had underactivation relative to controls in OFC/DLPFC, striatal, thalamic, and temporo-parietal regions, paralleling similar findings from the same study during motor inhibition (Page et al., 2009).

3.2.3 Summary of fMRI studies of cognitive control in ASD and OCD

The ASD literature broadly supports dorsolateral prefronto-striatal and ACC as well as parietal lobe reductions in ASD individuals during inhibitory control (Solomon et al., 2009, Vaidya et al., 2011, Solomon et al., 2014) and flexible attention (Schmitz et al., 2006, Shafritz et al., 2008). On the other hand, OCD studies, primarily in adults, support medial DLPFC and orbitofronto-striatal deficits during flexible attention (Sohn et al., 2000, Britton et al., 2010, Han et al., 2011). Moreover, studies in both adults and children with ASD (Kana et al., 2007, Shafritz et al., 2008, Solomon et al., 2009) and with OCD (Huyser et al., 2011) (Fitzgerald et al., 2005, Nakao et al., 2005, Rubia et al., 2010a, Rubia et al., 2011) have found abnormalities in the MPFC/ACC, but the direction of these abnormalities in clinical groups relative to controls is not consistent, possibly due to the effects of performance monitoring that are inherent in some of the tasks used to investigate inhibition. However, considering medial prefrontal regions' role in top-down executive control (MacDonald et al., 2000), one could hypothesize that both groups may show reduced activation in this region during tasks of cognitive control. Moreover, it is possible that ASD individuals may show more abnormalities in dorsolateral prefrontal regions (Schmitz et al., 2006, Shafritz et al., 2008, Solomon et al., 2009, Vaidya et al., 2011, Solomon et al., 2014), while individuals with OCD may show more temporo-parietal underactivation (Woolley et al., 2008, Page et al., 2009, Han et al., 2011). However, overall the literature is relatively inconsistent and more work is needed, particularly in larger samples, to fully understand the shared and disorder-specific mechanisms underpinning cognitive control in each disorder. Thus, Chapter 4 of this thesis presents a comprehensive review of whole-brain fMRI studies of cognitive control in ASD and OCD, as well as a comparative meta-analysis of reported functional activation differences between patients and controls in these studies.

3.3 Attention functions

3.3.1 fMRI studies of attention functions in ASD

Across all attention domains, it is probable that both bottom-up (i.e. environment-driven) and top-down (i.e. goal-driven) influences guide attention at some level. Corbetta & Shulman (Corbetta and Shulman, 2002) notably proposed that two distinct brain networks underlie the top-down and bottom-up modulation of attention. The bilateral dorsal fronto-parietal attention network comprises the frontal eye fields (FEF) and intraparietal sulcus (IPS) and is responsible for the voluntary control of attention, while a right-lateralised ventral fronto-parietal network comprising ventral PFC, anterior insula, middle frontal gyrus (MFG) and temporo-parietal junction (TPJ) is responsible for attention re-orienting based on environmental (i.e. bottom-up) information (Corbetta and Shulman, 2002, Corbetta et al., 2008).

During tasks of sustained attention and attention allocation in healthy adolescents (Rubia et al., 2009b, Rubia et al., 2009c) and adults (Lawrence et al., 2003), participants show activation in ventral and dorsal attention networks encompassing dorsolateral and inferior frontal, insular, parietal, occipital, striato-thalamic, and cerebellar regions and deactivation in regions of the so-called default mode network, comprising MPFC, ACC and posterior cingulate/precuneus. Furthermore, brain regions that are important for selective and sustained attention have been shown in three studies to be progressively more increased in activation with increasing age in developmental studies during attention-based tasks in adolescents and adults (Rubia et al., 2010b, Smith et al., 2011, Murphy et al., 2014). The first used a visuo-spatial selective attention task and showed that with increasing age, subjects had progressively enhanced activation in expected selective attention networks encompassing lateral fronto-striatal and temporo-parietal regions (Rubia et al., 2010b), in line with findings of an earlier

study of selective visual attention in ASD implicating abnormal parietal activation in ASD individuals compared to typically-developing controls (Belmonte and Yurgelun-Todd, 2003). The second used a CPT measuring sustained attention and similarly found that with increasing age, there was enhanced activation in inferior-frontal, temporo-parietal and cerebellar regions but decreased activation in posterior cingulate and insula (Smith et al., 2011). The third used the same psychomotor vigilance task used in this PhD and found that within the typically-developing control group, activation in dmPFC, bilateral insula and IFG, right striatal and bilateral temporo-parietal regions increased with increasing age (Murphy et al., 2014).

Only two fMRI studies have measured sustained attention in individuals with ASD using the psychomotor vigilance task described and used in Chapter 5 of this thesis. One study was in adolescents (Christakou et al., 2013b), and the other study investigated functional maturation of sustained attention brain networks in a combined group of adolescents and adults with ASD (Murphy et al., 2014). These studies found that individuals with ASD relative to typically-developing individuals had decreased activation in left DLPFC, striato-thalamic and parietal regions but increased activation in the cerebellum and precuneus, potentially reflecting poor deactivation of the proposed "task-negative" default-mode network (Christakou et al., 2013b). The investigation of functional maturation of sustained attention networks in ASD also found that typically-developing controls compared to ASD individuals - who did not show this pattern - had progressively enhanced activation with age in inferior and dorsolateral-prefrontal, striatal, temporal and cerebellar regions, suggesting that individuals with ASD may exhibit abnormal patterns of functional maturation within these networks from adolescence to adulthood (Murphy et al., 2014).

During selective attention, there is evidence for fronto-striatal, parietal and cerebellar fMRI abnormalities in adolescents with ASD (Allen and Courchesne, 2003, Gomot et al., 2006, Silk et al., 2006), with a study in adults showing similar results (Belmonte and Yurgelun-Todd, 2003). However, the subject numbers of these studies are quite low (N<10), so results should be interpreted with this caveat in mind. A relatively early ROI study comprising just eight individuals with ASD and eight matched controls between 14-38 years old on a target detection task showed reduced ipsilateral and contralateral cerebellar lobule VI activation in ASD participants relative to controls (Allen and Courchesne, 2003). Slightly later, Gomot and colleagues (Gomot et al., 2006) investigated a sample of twelve ASD adolescents between 10-15 years of age and posited that the phenotype of resistance to change (or, "need for sameness" (Kanner, 1943)) that is often observed clinically among individuals with ASD may be related to abnormal processing of unexpected stimuli, a function related to change-detection and attention. This study used an auditory oddball task and measured brain activation to the presentation of infrequently occurring stimuli. Consistent with the implication of the ACC in typically-developing participants outlined above, children with ASD showed reduced activation in this region after any stimulus presentation and reduced activation in bilateral temporo-parietal and right middle and inferior frontal regions compared to controls during presentation of novel stimuli (Gomot et al., 2006).

Fan et al. (Fan et al., 2005) proposed that attention can be conceptualised as three components: alerting, orienting and executive control, each of which have distinct underlying neural circuitry. Sustained attention and the ability to maintain vigilance to a specific stimulus fall within 'alerting' and are related most closely with the thalamus, TPJ, and other parietal regions that have been implicated in ASD (Fan et al., 2005). One theory of abnormal attention in ASD relates to the idea that individuals with ASD may fail to attend to salient, task-relevant stimuli but may also be easily distracted by subtle,

task-irrelevant stimuli (Keehn et al., 2016) and that this paradox as well as the over-focused selective attention observed clinically in ASD may be due to abnormal interactions among brain networks related to orienting and executive control of attention in ASD (Fan et al., 2012). This would suggest that perhaps alerting functions are relatively unaffected in ASD, but an ROI study testing this hypothesis showed that during alerting, ASD individuals had reduced activation relative to typically-developing controls in bilateral MFG and left caudate (Fan et al., 2012). Moreover, an ROI study of the intrinsic functional connectivity within sustained attention and default mode networks in ASD individuals found that there was no difference between ASD individuals and typically developing controls in the functional connectivity of the dorsal sustained attention network (Kennedy and Courchesne, 2008), although this study was conducted in a relatively small sample.

3.3.2 fMRI studies of attention functions in OCD

No fMRI studies have investigated sustained attention in OCD. Two studies investigated attention allocation in adolescents with OCD using inhibitory control tasks measuring the 'oddball' effect – that is, the effect the of low-frequency appearance of incongruent trials (Rubia et al., 2011). In the first study, although a Go/No-Go task was used to examine motor inhibition, ventromedial orbitofronto-striatal underactivation was observed in adult patients compared to controls, and the authors posited that this could be due to the attentional 'oddball' effect of the low frequency of target trials, suggesting abnormalities in sustaining attention (Page et al., 2009). Moreover, in this same study, temporo-parietal underactivation during a motor Stroop task was related to attentional network dysfunction in OCD, as motor versions of the Stroop task used place a high demand on visuo-spatial attention mechanisms, in line with previous neurocognitive studies of selective attention deficits in OCD (Chamberlain et al., 2005).

A later study using a Simon oddball task found that adolescents with OCD had reduced activation in right DLPFC compared to controls and adolescents with ADHD during 'oddball' incongruent trials, extending the implication of dorsolateral prefrontal regions in higher-level EF to simpler perceptual and attention allocation functions in OCD (Rubia et al., 2011).

3.3.3 Summary of fMRI studies of attention functions in ASD and OCD

Attention functions have been investigated in both ASD and OCD, although a focus in the fMRI literature specifically on sustained attention and vigilance is somewhat sparse in these disorders, especially OCD, despite the implication of neurocognitive sustained attention deficits in both ASD (Murphy et al., 2014, Chien et al., 2015) and OCD (Mataix-Cols et al., 1997, Benzina et al., 2016). There are findings of dorsolateral prefronto-striatal and ACC reductions in ASD (Gomot et al., 2006) and OCD individuals (Rubia et al., 2011) during sustained attention on e.g. oddball tasks. Moreover, temporo-parietal and cerebellar reductions have been implicated in ASD (Allen and Courchesne, 2003) during attention, but similar temporo-parietal dysfunction has only been observed in OCD as an oddball effect during inhibitory control tasks (Page et al., 2009). On the other hand, the two OCD studies, both in adolescents, support DLPFC and orbitofronto-striatal deficits during attention allocation (Page et al., 2009, Rubia et al., 2011). Taken together, these results suggest that characteristics of dorsolateral and inferior fronto-striatal network abnormalities during a range of attention functions may be seen in both ASD and OCD, but that cerebellar and default-mode attention network dysfunction may be more closely related to ASD, while ventrolateral and orbitofronto-striatal network abnormalities may be more specifically related to OCD. However, in the face of neurocognitive deficits in attention in both ASD and OCD, there is a relative lack of fMRI investigations of attention functions,

particularly in OCD, as well as heterogeneity in tasks tapping different but related aspects of attention. More work is warranted to parse apart the specific shared or disorder-specific neural correlates underlying sustained attention. An understanding of the shared and disorder-specific neural correlates of sustained attention is important for comparing and delineating the underlying mechanisms of attention in these disorders, but no studies have yet made this comparison. For these reasons this PhD compared the neurofunctional activation in ASD and OCD during a task of sustained attention; Chapter 5 of this thesis presents an fMRI comparison of boys with ASD and boys with OCD on a psychomotor vigilance task of sustained attention.

3.4 Reward-related decision-making

3.4.1 fMRI studies of temporal discounting and related functions in ASD

It is important to first note that that while 'reward processing' can be broadly investigated as a neurocognitive construct, there are vast differences in tasks tapping different aspects of reward processing, and other processes such as attention, learning and WM may be also be involved across these tasks. There are few fMRI studies in both ASD and OCD, and even fewer in children, that have used the same tasks described in later chapters of this PhD to specifically investigate the same neurocognitive aspects of reward processing (e.g. TD and gambling tasks). Therefore, conclusions regarding the neural correlates of these processes based on the existing literature should be made with much caution, as heterogeneity is likely due to differences in tasks and the specific aspects of reward processing they are investigating.

However, keeping this caveat in mind, fMRI studies of TD in healthy adults and children implicate ventromedial and orbitofrontal fronto-limbic networks important for reward-based decision-making, and dorsolateral and inferior-fronto-insular-striato-

parietal networks implicated in temporal foresight (Christakou et al., 2011, Peters and Büchel, 2011, Chantiluke et al., 2014b, Wesley and Bickel, 2014). More specifically, an Activation Likelihood Estimation (ALE) meta-analysis of 18 fMRI studies of TD in healthy children and adults found that TD tasks reliably activated the striatum, insula, anterior and posterior cingulate, and fronto-cortical regions including lateral PFC and IFG (Wesley and Bickel, 2014).

Despite some behavioural studies showing that ASD individuals discount rewards at similar rates to their typically-developing peers during TD (Antrop et al., 2006, Demurie et al., 2012, Chantiluke et al., 2014b), ventromedial and fronto-limbic neural circuitry critically important for successful TD (Peters and Büchel, 2011) has been shown to be abnormal during related reward anticipation tasks such as monetary incentive delay (Knutson et al., 2001) and rewarded Go/No-go tasks measuring impulsivity in ASD (Dichter et al., 2012c, Kohls et al., 2013). There has been only one fMRI study investigating the neural correlates of TD in adolescents with ASD (Chantiluke et al., 2014b). This study investigated neural activity in adolescents with ASD with and without co-morbid ADHD and found that, in addition to worse (steeper) overall TD performance in the non-comorbid ASD group, better (less-steep) TD was associated with activation during delayed choices in left inferior parietal lobe (IPL) reaching into pre- and post-central gyri and in right cerebellum, suggesting a disorder-specific phenotype of TD that does not overlap with ADHD. Moreover, in between-group comparisons investigating relationships between brain activation and TD performance, ASD adolescents had weaker brain-behaviour correlations in bilateral superior temporal lobes (STL) and right insula/IFC but stronger correlations in left IPL relative to typically-developing controls (Chantiluke et al., 2014b). Abnormalities in these regions important for TD could suggest problems with forward planning in ASD, which has been evidenced behaviourally in other studies (Hill, 2004).

Other fMRI studies have investigated reward processing involving monetary incentives in ASD. One validated construct within which to investigate anticipation of immediate reward and/or punishment is the monetary incentive delay task, known to reliably activate fronto-striato-thalamic reward circuitry (Knutson et al., 2001). Dichter and colleagues (Dichter et al., 2012c) investigated adult males with ASD during a monetary incentive delay task and found that ASD individuals had reduced activation in BG regions including left nucleus accumbens (NAcc) and right putamen as well as frontal regions including ACC and left insula during reward anticipation relative to typically-developing participants. During monetary outcomes, ASD participants had reduced activation relative to control participants in left NAcc, right frontal pole and right insula, but interestingly did not show abnormal activation relative to controls in VMPFC regions typically implicated in reward and TD-related circuitry (Peters and Büchel, 2011). However, the task used in this study distinguished between monetary and object-based rewards and showed that ASD individuals' brain activation during anticipation did not differ between reward types compared to controls but during anticipation, ASD individuals had higher VMPFC activation to object rather than monetary rewards (Dichter et al., 2012c), suggesting a possible insensitivity specifically to monetary rewards, supported by the findings of (Demurie et al., 2012) which showed no behavioural differences between ASD individuals and controls during monetary reward processing. Another study investigating reward-related activity to social and non-social (monetary) rewards during a rewarded go/no-go task in adolescent boys with ASD showed that ASD boys had underactivation relative to control boys during rewarded conditions in reward-related meso-cortico-limbic regions including thalamus, amygdala, striatum, Nacc, and ACC in whole-brain analyses (Kohls et al., 2013), in line with (Dichter et al., 2012c). Moreover, ROI analyses revealed that ACC and amygdala were hypoactivated to both monetary and social rewards. In line with this, a study in

adults with ASD found that ASD participants had decreased bilateral NAcc activation during presentation of social rewards, but not monetary rewards, compared to controls and that this abnormality was shared with social anxiety patients (Richey et al., 2012). However, this is in contrast to a previous study showing reduced VS activation to social (but not non-social) rewards in boys with ASD (Scott-Van Zeeland et al., 2010b). It has been suggested that the NAcc plays a role in incentive motivation, salience and feelings of 'wanting' (Peciña, 2008), thus suggesting aberrant reward salience processing in this region in individuals with ASD, although the specificity of this abnormality with regard to salience of different reward types remains to be clarified.

Interestingly, in a study examining brain activation of ASD children during presentation of food-based rewards, ASD individuals showed increased response in bilateral insula and ACC relative to their typically-developing peers (Cascio et al., 2012b), alternatively suggesting that neural response to primary reward is not diminished but rather is enhanced in children with ASD. Functional subdivisions in the insula can be investigated along a posterior-anterior gradient of interoceptive awareness, where posterior regions respond to a stimulus's objective features, whereas anterior regions respond to subjective assessment of these features and their emotional significance (Craig, 2009). Thus, somewhat in contrast to the findings of (Kohls et al., 2013), these results could suggest that individuals with ASD may attribute higher emotional value to rewards compared to typically-developing participants, in line with the insula's role in interoception (Craig, 2003).

In line with findings from Casio and colleagues (Cascio et al., 2012b), Schmitz et al. found that during a rewarded version of the CPT, men with ASD had enhanced activation in left ACC compared to control participants in a small (N=10) sample (Schmitz et al., 2008). Moreover, this activation was negatively correlated with social

interaction scores as assessed by the ADI. The authors posited that this finding could be indicative of an increased need for feedback-related performance monitoring in ASD or enhanced attention to rewarded stimuli (Schmitz et al., 2008).

Planning is an EF construct that is also implicated in temporal foresight. The only two studies to investigate the neural correlates of planning in ASD adults used the Tower of London task and found decreased activation in frontal regions including middle, superior and inferior frontal cortex and IPL but increased activation in limbic regions including right hippocampus and thalamus, and in left lingual gyrus, with pronounced fronto-parietal under-connectivity compared to controls during planning in individuals with high-functioning ASD (Just et al., 2007, Just et al., 2012).

3.4.2 fMRI studies of gambling and reward learning in ASD

No fMRI studies have investigated gambling or used the IGT in ASD populations. However, there have been studies investigating reward-based reinforcement and implicit learning in autism, functions that are closely linked to abilities on the IGT. In a reversal-learning task (a reward-based learning task requiring reinforcement learning and flexible choice behaviour), adolescents with ASD had decreased medial prefrontal and precuneus activation relative to typically-developing children (Chantiluke et al., 2015a). Moreover, a later study in adults with ASD supports and extends these findings; during reversal learning, adults with ASD showed reduced brain activation specifically when outcomes were uncertain in cognitive decision-making regions including frontal motor planning systems (e.g. left DLPFC, premotor cortex), cognitive subdivisions of the ACC, and the parietal cortex and in areas supporting reinforcement learning, including the ventral striatum, thalamus, and the affective subdivision of the ACC (D'Cruz et al., 2016). These findings suggest that abnormal dorsolateral and medial prefrontal activation in ASD individuals may not

simply be altered when reward-based choice shifts are required, but that these abnormalities occur when learned choices must be inhibited and the outcomes of new choices are uncertain.

Collectively, these results suggest that ASD individuals exhibit abnormalities in medial prefronto-striato-thalamic and fronto-parietal regions important for reward processing, decision-making and reinforcement learning, and that aberrant interactions in these networks may contribute to difficulties in flexible choice responses. This evidence is in line with behavioural rigidity that is observed clinically in ASD but is somewhat in contrast to findings in behavioural studies using the IGT which show that ASD individuals tend to be less consistent in their choices (Johnson et al., 2006, Yechiam et al., 2010) or even perform better compared to controls during gambling tasks (South et al., 2014). Further research is needed to probe the neural correlates of reinforcement learning in ASD to fully disentangle these brain-behaviour relationships, but one could hypothesise that ASD individuals would show abnormal activation in similar MPFC-striato-thalamic and fronto-parietal brain regions during the IGT.

3.4.3 fMRI studies of temporal discounting and related functions in OCD

Impaired reward processing has been suggested to be a key neurocognitive deficit in OCD (Salkovskis, 1985, Graybiel, 2000, Cavedini et al., 2006). This hypothesis is based on initial evidence that orbitofronto-striato-thalamo-orbitofrontal loops important in reward perception and decision-making are implicated in the pathophysiology of OCD (Cavedini et al., 2006, Menzies et al., 2008). More recent theories suggest that OCD-related cognitive impairments may be a result of disruptions in the balance between goal-directed and habit-based learning systems important for reward-based decision-making (Gillan et al., 2011, Gillan and Robbins, 2014). Evidence from neuroimaging studies theoretically supports this, given that functional

neurocircuitry implicated in reward-processing overlaps to a large degree with regions that are commonly linked to the pathophysiology of OCD, including ventromedial and orbitofrontal cortical regions, and the BG, thalamus and ACC, as well as DLPFC (Saxena and Rauch, 2000, Kwon et al., 2009) (and as reviewed in Chapter 4). As mentioned previously, the VS, specifically the NAcc, is particularly important for reward-related functions (Haber and Knutson, 2010), and abnormal function in this region has been implicated in OCD in a meta-analysis of 13 PET and SPECT studies showing consistent differences in radiotracer uptake in the ventral striatum of adult OCD patients (Whiteside et al., 2004). Despite broad evidence for neurofunctional abnormalities in reward circuitry of individuals with OCD, no previous fMRI studies have specifically investigated the neural correlates of TD in OCD. There have, however, been a number of fMRI studies investigating reward and incentive processing in OCD, albeit mostly in adult samples. The first fMRI study to investigate reward circuitry function in adults with OCD used the monetary incentive delay task (Knutson et al., 2001) and found that during reward anticipation, OCD patients had reduced activation in NAcc, but that brain activation did not differ between patients and controls during reward receipt (Figee et al., 2011). However, two other studies (which had overlapping samples of participants) using versions of this task in adults with OCD found that brain activation of patients did not differ from that of control participants during reward anticipation (Jung et al., 2011, Choi et al., 2012). Jung and colleagues further showed that OCD patients relative to controls had increased activation in fronto-striatal regions including putamen, pre-central gyrus, posterior insula and ACC as well as cerebellum only during reward receipt, and that enhanced VS activation in patients versus controls was evident only during loss-avoidance conditions (no loss vs. loss contrast) which was furthermore correlated with severity of compulsions (Jung et al., 2011). More recently, Kaufmann et al. (Kaufmann et al., 2013) found that adults with OCD had reduced

superior and medial prefrontal activation during reward anticipation but enhanced activation in this region during loss-avoidance relative to controls, presenting further evidence in line with (Jung et al., 2011) for fronto-striatal abnormalities driving loss-aversion styles of reward-processing in OCD. It is possible that these differences in findings are related at least in part to sample heterogeneity, as many of the patients were on medication or had comorbid psychiatric conditions, and duration of illness also differed between studies.

The Tower of London task is commonly used to investigate disturbances in the fronto-striatal circuitry involved in planning processes implicated in TD (van den Heuvel et al., 2003). Three fMRI studies have used this task to study planning in adults (van den Heuvel et al., 2005b, van den Heuvel et al., 2011) and adolescents (Huyser et al., 2010) with OCD. The earliest of these studies found that in addition to significant behavioural impairments in planning, medication-free adults with OCD had reduced activation relative to controls in DLPFC and caudate nucleus (van den Heuvel et al., 2005b). A later study from the same group compared these OCD patients to patients with panic disorder and hypochondriasis and found that all patient groups (OCD patients as well as patients with related disorders including panic disorder and hypochondriasis) had decreased activation in precuneus, caudate nucleus, globus pallidus and thalamus compared to control participants, in line with the earlier 2005 study but suggestive of a possible shared phenotype across different but related clinical populations. A study using a parametric version of this planning task in medication-free adolescents with OCD (many of whom had a comorbid anxiety disorder) supports prefrontal deficits, as this study found that adolescent patients relative to controls had decreased activation in left posterior DLPFC/premotor cortex and right parietal lobe (Huyser et al., 2010). Moreover, with increasing task difficulty, OCD adolescents activated additional frontal brain regions including dorsomedial PFC (dmPFC), dorsal

ACC and insula. These findings support neurobiological models of OCD outlined by reduced activation in dorsal-frontal-parietal-striatal cognitive networks and hyperactivity in medial prefrontal limbic affective circuitry (Menzies et al., 2008).

3.4.4 fMRI studies of gambling and reward learning in OCD

While no fMRI studies have investigated the neural correlates of the IGT or gambling behaviour in OCD, a number of studies have examined reward-based learning and cognitive flexibility in OCD. Reduced activation in dorso- and ventrolateral and orbitofrontal PFC and ACC as well as the parietal cortex during reversal learning in OCD patients relative to controls has been shown in a number of adult studies (Remijnse et al., 2006, Chamberlain et al., 2008, Gu et al., 2008). Reduced lateral PFC and OFC activation has also been observed in unaffected relatives of individuals with OCD (Chamberlain et al., 2008), suggesting that this pattern of activation during reward learning may be a candidate endophenotype of the disorder. In another study, underactivation in these regions in OCD was related to worse performance on tasks requiring cognitive flexibility (Remijnse et al., 2009). Moreover, the task used by Remijnse and colleagues (Remijnse et al., 2006) in unmedicated adults with OCD found that upon reward (but not punishment) receipt, patients showed decreased activation compared to controls in right medial and lateral OFC and right caudate.

One study examined learning processes in twelve adolescents with OCD using fMRI (Lázaro et al., 2008). This study used an implicit learning serial reaction time task where subjects were required to learn motor responses to complex and simple sequences. The task is designed to tap cortico-striatal regions (Rauch et al., 1997b), and this study found that OCD adolescents had hyperactivation in bilateral middle frontal gyrus, possibly as a compensatory mechanism for striatal dysfunction that, although not

observed in this study, is commonly seen in OCD during implicit learning (Rauch et al., 2000).

Taken together, these results suggest that diminished activation in paralimbic and dorsolateral, ventromedial and ACC frontal-executive brain regions in OCD may be related to impairments in both emotional and cognitive aspects of reward-based decision-making in the disorder (Rauch et al., 2000, Remijnse et al., 2006). In healthy individuals, OFC and VMPFC activation has been linked to reward-related aspects of behavioural control (Breiter et al., 2001). Thus, abnormalities in these regions could hypothetically relate to clinical symptoms of the obsessive-compulsive cycle in OCD, as it has been suggested that OCD patients feel insufficient reward from performing compulsions (Fineberg et al., 2009), although this theory has not been formally tested.

3.4.5 Summary of fMRI studies of reward-related decision-making in ASD and OCD

While there is not yet a general consensus among findings in the neuroimaging literature of specific profiles of activation in ASD and OCD, one can draw broad conclusions regarding the brain regions involved in aberrant reward processing and decision-making in both disorders. In line with the involvement of ventromedial, fronto-limbic and fronto-striatal regions in reward processing and decision-making in healthy populations (Peters and Büchel, 2011), it has been shown that both ASD (Dichter et al., 2012c, Kohls et al., 2013, Chantiluke et al., 2015a) and OCD (Jung et al., 2011, Choi et al., 2012) exhibit abnormalities in these circuitries. However, there have also been studies that did not find abnormal ventromedial prefrontal activation in individuals with ASD or OCD relative to control participants, possibly due to study sample heterogeneity (Demurie et al., 2012, Dichter et al., 2012c).

Some findings have emerged suggesting abnormalities that may be specific to ASD. For example, abnormalities in cerebellar regions have been implicated during reward-based decision-making and TD in ASD adolescents (Chantiluke et al., 2014b), but there is little evidence to support cerebellar involvement in decision-making abnormalities in OCD. Parietal regions may also be abnormal during reward learning in ASD (Chantiluke et al., 2014b, D'Cruz et al., 2016), a finding which has not consistently been reported in the OCD literature. Moreover, studies have suggested that ASD individuals may be more sensitive to non-social rewards, and this may be a factor in studies that do not find differences between ASD individuals and controls during reward processing (Demurie et al., 2012, Dichter et al., 2012c), while OCD individuals may be less sensitive to specificity of reward types, although no studies have specifically investigated this in OCD. Thus, it can be hypothesised that compared to OCD patients, ASD individuals may have more pronounced abnormalities in cerebellar, striatal and parietal regions but that OCD patients may have specific abnormalities in OFC regions during reward-based decision-making. However, no studies have formally tested this comparison. The aim of this PhD was therefore to test this hypothesis by comparing the two disorders on tasks of gambling and TD. Thus, Chapter 6 of this thesis investigates shared and disorder-specific functional brain abnormalities during TD, and Chapter 7 tests this comparison during the IGT in boys with ASD and with OCD compared to typically-developing control boys.

3.5 Other cognitive domains

3.5.1 ASD

Working memory impairments have been found in neurocognitive studies of ASD across all ages (Koshino et al., 2005, Williams et al., 2005, Steele et al., 2007,

Geurts and Vissers, 2012, Fried et al., 2016). fMRI studies have also investigated the neural correlates of WM in adolescents with ASD (Silk et al., 2006, Chantiluke et al., 2014a, Vogan et al., 2014, Rahko et al., 2016). Broadly, prefrontal, premotor, dorsal ACC, striatal and posterior parietal activation has been associated with WM in healthy populations (Owen et al., 2005), and studies of WM in ASD on a range of WM tasks have generally found impairments in these regions in both children and adults with ASD (Luna et al., 2002, Koshino et al., 2005, Silk et al., 2006, Chantiluke et al., 2014a, Rahko et al., 2016). Thus, keeping in mind caveats that many of these studies are based on ROI analysis and small sample sizes, it can be concluded that adolescents with ASD have been shown to have decreased activation in right fronto-striatal regions during spatial WM (Silk et al., 2006) and N-back tasks (Chantiluke et al., 2014a). Adults with ASD have also been shown to have decreased activation during verbal WM in predominantly left-hemispheric regions including left inferior/middle frontal cortex, IPL and bilateral DLPFC, but increased activation in right-hemispheric areas including right superior/inferior frontal cortex and right superior/inferior parietal lobe (Luna et al., 2002, Koshino et al., 2005).

As stated in Chapter 1, children with ASD have difficulties with mentalising, ToM, mental state attribution and social interactions. There has been much fMRI research investigating the neural correlates of socio-emotional processing and ToM in ASD. Studies investigating irony comprehension using vocal and facial expressions have found decreased activation in areas typically associated with ToM, including medial prefrontal cortex (mPFC) (Gallagher and Frith, 2003, Völlm et al., 2006). On these tasks, increased activation in ASD individuals compared to controls has also been observed in bilateral temporal regions and right IFC in whole-brain and ROI studies (Wang et al., 2006, Wang et al., 2007). Moreover, investigations of ToM and mentalising difficulties in children with ASD have largely found similar reductions in

regions typically associated with the "social brain" network (Blakemore, 2008), including IFG, TPJ, mPFC and temporal poles (Castelli et al., 2002, Mason et al., 2008, Lombardo et al., 2011, Holt et al., 2014, Jack and Morris, 2014, Kana et al., 2014, O'Nions et al., 2014). Moreover, many (but not all) studies of face processing in ASD implicate hypoactivation in similar regions, as well as the fusiform gyrus and amygdala, as reviewed in (Dichter, 2012). This collective evidence provides support that children with ASD have neurofunctional abnormalities in the brain networks associated with ToM (Gallagher and Frith, 2003, Blakemore, 2008).

In line with the "weak central coherence" neuropsychological theory in ASD (Happé, 1997), whole-brain (Manjaly et al., 2007, Spencer et al., 2012b) and ROI (Lee et al., 2007, Spencer et al., 2012a) fMRI studies using the embedded figures task (Shah and Frith, 1983) to investigate central coherence in adolescents with ASD have found reduced deactivation of the default mode network, as well as reduced activation in regions associated with central coherence, including dorsal premotor cortex, right superior parietal lobe, and left occipital lobe (Lee et al., 2007, Manjaly et al., 2007, Spencer et al., 2012a, Spencer et al., 2012b). In adults, reduced activation in parietal regions and right DLPFC as well as increased right occipital and inferior temporal activation was also found in an early study (Ring et al., 1999). Interestingly, one whole-brain study in adolescents found increased activation in ASD participants compared to controls in left middle temporal gyrus, bilateral superior temporal sulcus, left IFG, and right inferior temporal gyrus (Spencer et al., 2012b). Given this discrepancy, it should be noted that task and control conditions vary widely among studies in ASD using the embedded figures task (Spencer et al., 2012b).

3.5.2 OCD

fMRI studies have investigated the neural correlates of working memory in adults with OCD (van der Wee et al., 2003, Shin et al., 2006, van der Wee et al., 2007, Henseler et al., 2008, Nakao et al., 2009a, Koch et al., 2012, de Vries et al., 2014, Diwadkar et al., 2015), but none have done so in children or adolescents. While some of these studies provide evidence for neuropsychological impairments on WM tasks (van der Wee et al., 2003, Shin et al., 2006), others do not (Henseler et al., 2008, Nakao et al., 2009a, Koch et al., 2012), with visuo-spatial memory impairments more consistently reported in OCD compared to verbal memory (Kuelz et al., 2004). Both increased and decreased WM-related activation of the ACC (van der Wee et al., 2003, Shin et al., 2006, Koch et al., 2012) and DLPFC (Shin et al., 2006, Nakao et al., 2009a, de Vries et al., 2014) has been observed in OCD, particularly under high cognitive demands. Moreover, hyperactivity in premotor cortex and IFG has also been reported (Henseler et al., 2008, Koch et al., 2012). However, neurofunctional correlates of WM may change with age, so it is important to investigate these processes in younger populations with OCD, particularly given the relevance of WM to other reward-based functions that have been shown to be dysfunctional in adolescents with OCD (Menzies et al., 2008).

Given that a core feature of OCD is that patients spend a significant portion of their time engaging in rituals and compulsions, it is important to understand the neurobiological basis of symptom provocation. The earliest fMRI study investigating symptom provocation in OCD used an ROI approach and had a very small number of participants but showed that adults with OCD had activation in medial orbitofrontal, lateral frontal, anterior cingulate, anterior temporal and insular cortices, as well as subcortical striato-limbic regions including caudate and amygdala (Breiter et al., 1996) during symptom provocation. It is critical to note that this study did not directly

compare OCD individuals to control subjects. Nonetheless, this study provided the first evidence of possible hyperactivity in medial and lateral fronto-striatal circuitry during symptom provocation. Indeed, ROI case-control comparisons have subsequently shown similar hyperactivation in adults with OCD during symptom provocation (Simon et al., 2010, Simon et al., 2014), extending earlier meta-analysis findings combining 8 fMRI and PET studies which showed significant activation likelihood in orbitofrontal and ACC loops and a left dorsal fronto-parietal network, including DLPFC, precuneus, and left superior temporal gyrus (Rotge and Tignol, 2008). This hyperactivation was also supported in a review (Nakao et al., 2014), but Nakao and colleagues importantly highlight the possibility that this activation may differ among different symptom dimensions in OCD, as previously demonstrated by (Mataix-Cols et al., 2004). Interestingly, the results of the only fMRI study to investigate symptom provocation in paediatric OCD are in contrast with the above evidence of hyperactivation. This ROI study (Gilbert et al., 2009) looked at both contamination-based and symmetry-based symptoms and showed reduced activation in children with OCD compared to controls in right insula, putamen, thalamus, DLPFC, and left OFC as well as right thalamus and insula, suggesting potential developmental effects on the neural systems underlying symptom dimensions in OCD.

3.6 Overall summary and conclusions

This chapter has reviewed the neurofunctional abnormalities that have been observed in adolescents, as well as adults, with ASD and those with OCD during tasks of inhibition, cognitive control, sustained and selective attention, as well as reward processing and reward-based decision-making, including tasks of TD, gambling, planning and reward learning. Because of study limitations such as heterogeneous samples, small sample numbers, variation in medication status of patients, ROI versus

whole-brain approaches, and differences in tasks used to investigate these varied processes, as well as a general dearth of child/adolescent fMRI studies in these areas, it is somewhat difficult to produce a consolidated hypothesis regarding neurofunctional differences and similarities between ASD and OCD. Small sample sizes yield less statistical power to detect between-group differences, particularly in behavioural tasks but also in neurofunctional activation (Thirion et al., 2007), and psychiatric comorbidities such as anxiety in OCD (Mataix-Cols et al., 2005) and ASD (White et al., 2009) can limit disorder-specific interpretations of findings. Moreover, psychiatric medication such as SSRIs have neurofunctional effects that may confound fMRI results (Murphy, 2010). Lastly, there is substantial evidence of sexual dimorphism in brain development (Sowell et al., 1999, Giedd and Rapoport, 2010), so single-sex matched groups should be investigated to elucidate any sex-specific effects. This is particularly relevant to ASD, as there is evidence to suggest that clinical, cognitive and neurobiological correlates of ASD greatly differs between males and females (Baron-Cohen, 2002, Baron-Cohen et al., 2011, Dworzynski et al., 2012).

However, keeping these caveats in mind, it is possible to draw general conclusions and formulate hypotheses regarding the neurofunctional mechanisms underlying attention and reward-based decision-making in ASD and OCD and the features that may be shared or disorder-specific.

Although findings among the fMRI literature in ASD are still relatively inconsistent, some conclusions can be drawn from reviews of the paediatric literature (e.g. (Dichter, 2012)) regarding a) abnormal fronto-striatal activation in DLPFC and BG during cognitive control, possibly relating to attention problems and the maintenance of RRBIs, b) hypoactivation in "social brain" regions including TPJ, IPS, amygdala and IFG during tasks of affective salience and social relevance, and c) abnormal lateral,

medial and inferior prefrontal, as well as mesolimbic (e.g. VS, amygdala) activation to rewards. Moreover, the fMRI literature supports cerebellar and temporo-parietal involvement in attention functions that may be more specifically related to inattention in ASD compared to OCD (Allen and Courchesne, 2003, Schmitz et al., 2006, Shafritz et al., 2008), although limited evidence for temporo-parietal dysfunction during attention tasks has also been observed during cool EF and attention functions in OCD (Chamberlain et al., 2005, Page et al., 2009). Thus, a comparison on brain function during cool EF and attention tasks is necessary to clarify the degree to which these abnormalities are shared or disorder-specific in ASD and OCD.

While several models have been proposed which implicate hyperactivity within orbitofronto-striato-thalamo-cortical networks in OCD (Saxena et al., 1998b, Baxter, 1999, Aouizerate et al., 2004, Kuelz et al., 2004, Menzies et al., 2008), particularly during symptom provocation (Rotge and Tignol, 2008, Nakao et al., 2014), recent reviews have called these models into question, providing evidence of hypoactivation in similar networks during cool EF (e.g. inhibitory control (Norman et al., 2016)). Furthermore the involvement of dorsolateral prefrontal and ACC regions as well as regions outside these CTSC networks such as the parietal cortex and amygdala may be implicated in OCD in structure as well as during EF tasks of planning, working memory, decision-making and inhibitory control (Maltby et al., 2005, van den Heuvel et al., 2005b, Menzies et al., 2008, Szeszko et al., 2008, Nakao et al., 2014). Moreover, there may be developmental effects on brain function, with some studies suggesting that abnormalities in OFC and caudate nucleus are more closely associated with adult OCD, while putamen and globus pallidus as well as thalamus abnormalities may be more distinctly implicated in paediatric OCD in both structure and function (Ornstein et al., 2010, Brem et al., 2012, deWit et al., 2014).

These inconsistencies suggest that these models are not sufficient for wholly explaining neurocognitive deficits observed across OCD. This thesis proposes that comparing brain function and structure in OCD with other disorders such as ASD which commonly exhibit shared neurocognitive deficits is key in understanding shared and disorder-specific features in each disorder and is a critical next step for improving models of neuropsychiatric abnormalities.

EF, including cognitive control and decision-making, has been closely associated with dorsolateral and ACC loops in healthy populations during error monitoring and the allocation of cognitive control resources during decision-making (Miller and Cohen, 2001). Moreover, parietal regions seem to be important for attention functions, implicated in the switching of attention focus (Corbetta and Shulman, 2002). Given that children with ASD (Dichter, 2012) and OCD (Menzies et al., 2008) have been shown to have abnormal function in these regions during a range of hot and cool EF, this could suggest a possible shared neurofunctional mechanism underlying attention and decision-making behaviour in each disorder, providing evidence of overlap in both impulsive and compulsive phenotypes in each disorder. However, vast inconsistencies exist in the literature, very few studies in paediatric populations have been conducted, and no studies have compared ASD and OCD directly on measures of EF, whether behavioural or neurofunctional. This work is critically needed to elucidate shared and disorder-specific aspects underlying symptoms.

This PhD focuses on neurocognitive constructs that have been shown to be abnormal in both ASD and OCD individuals: (i) cognitive and inhibitory control, (ii) sustained attention, (iii) temporal foresight, and (iv) gambling. There is evidence in ASD that the neural correlates of impairments in both cool and hot EF are abnormal compared to typically-developing individuals. In OCD, there is similarly evidence of

neurocognitive impairments compared to control subjects, but less is known about consistent neural underpinnings of these deficits, particularly in adolescents. This thesis first provides a review and meta-analysis of whole-brain fMRI studies of cognitive control and structural (VBM) neuroimaging across paediatric and adult studies of individuals with ASD or OCD (Chapter 4). Based on existing literature within each disorder, I hypothesised that OCD patients would show structural and functional dysregulation within medial prefrontal CSTC networks, specifically decreased ACC, OFC and mPFC but increased BG volumes and activation (Radua et al., 2010, van Velzen et al., 2014), while individuals with ASD would show reductions in lateral fronto-striato-limbic volume and activation (Via et al., 2011, DeRamus and Kana, 2015).

The following experimental chapters present data from fMRI studies where adolescent boys with ASD, with OCD, and typically-developing control boys completed computerised cognitive tasks in the scanner measuring sustained attention (Chapter 5), temporal discounting (Chapter 6), and gambling (Chapter 7). Behavioural and neurofunctional similarities and differences were compared between ASD and OCD, with the aim of elucidating the neurobiological basis of overlapping and disorder-specific cognitive deficits. Given prior evidence from fMRI studies during attention tasks, I hypothesised that during sustained attention, both ASD and OCD would exhibit dorsolateral and inferior fronto-striatal as well as fronto-parietal abnormalities, but that cerebellar and default-mode attention network dysfunctions would be more closely related to ASD, while orbitofrontal-striatal network abnormalities would be more specifically related to OCD (Sohn et al., 2000, Gomot et al., 2006, Schmitz et al., 2006, Shafritz et al., 2008, Page et al., 2009, Britton et al., 2010, Han et al., 2011, Rubia et al., 2011). Based on evidence of disorder-specific abnormalities during TD in ASD boys (Chantiluke et al., 2014b), I hypothesised similar disorder-specific impairments relative

to OCD during TD. Moreover, I hypothesised that both patient groups would show underactivation in ventromedial prefrontal, limbic and striatal regions implicated in TD and reward-based decision-making (Fineberg et al., 2009, Chantiluke et al., 2015a, Grassi et al., 2015, Chen et al., 2016), but that dorsolateral prefrontal dysfunction would be specific to OCD boys (Menzies et al., 2008, Norman et al., 2016), while insular and temporo-parietal dysfunction would be related to ASD (Di Martino et al., 2009, Chantiluke et al., 2014b). Finally, during the IGT, I hypothesised that ASD individuals would uniquely show less choice consistency based on prior evidence of similar behavioural impairments (Johnson et al., 2006, Yechiam et al., 2010, Mussey et al., 2015). Moreover, given that both disorders have shown neurofunctional deficits during reward processing and reward-based decision making in ventromedial-fronto-temporo-limbic and orbitofronto-striatal reward systems, I hypothesised that boys with ASD and with OCD would show reductions in these regions during the IGT, but that orbitofrontal deficits would be more pronounced in OCD while ventral striatal and anterior cingulate deficits would be more pronounced in ASD (Menzies et al., 2008, Kohls et al., 2013), suggesting shared and disorder-specific trans-diagnostic mechanisms for hot EF impairments. Understanding the overlapping and disorder-specific neural mechanisms underlying these neurocognitive deficits in both disorders is a critical step towards understanding how these disorders differ at the neurobiological level, as well as elucidating trans-diagnostic phenotypes that may be common to both disorders.

CHAPTER 4 - COMPARATIVE MULTIMODAL META-ANALYSIS OF STRUCTURAL AND FUNCTIONAL BRAIN ABNORMALITIES IN AUTISM SPECTRUM DISORDER AND OBSESSIVE-COMPULSIVE DISORDER

This chapter is presented as the final accepted manuscript version of the published peer-reviewed journal article:

Carlisi, CO, Norman, LJ, Lukito, SS, Radua, J, Mataix-Cols, D, Rubia, K. Comparative Multimodal Meta-analysis of Structural and Functional Brain Abnormalities in Autism Spectrum Disorder and Obsessive-Compulsive Disorder (2016). *Biological Psychiatry*, 82(2): 83-102.

DOI: http://dx.doi.org/10.1016/j.biopsych.2016.10.006

4.1 Introduction

Autism spectrum disorder (ASD) is a predominantly male neurodevelopmental disorder characterised by difficulties in reciprocal social-communication and stereotyped repetitive behaviours (American Psychiatric Association, 2013) with a prevalence of 0.6-1% (Baird et al., 2006).

Obsessive-compulsive disorder (OCD) is characterized by recurrent intrusive and distressing thoughts (obsessions) and repetitive mental and behavioural rituals (compulsions) (American Psychiatric Association, 2013), affecting 1-3% of the population, with a slightly higher prevalence among paediatric males and adult females (Ruscio et al., 2010).

Both disorders are highly heterogeneous (Wiggins et al., 2012), carry more than 25% comorbidity with one another (Russell et al., 2005) and can be clinically difficult to separate. Both disorders are thought to be associated with poor top-down behavioural and neurocognitive inhibitory control (Robbins et al., 2012), which may underlie poor

control over stereotyped repetitive behaviours in ASD (Geurts et al., 2014) and compulsions and intrusive thoughts in OCD (van Velzen et al., 2014). Inhibitory control is typically measured in motor and interference inhibition or switching tasks (Aron, 2011). Motor response inhibition tasks including go/no-go (GNG) and stop tasks measure selective inhibition or withdrawal of a built-up pre-potent response to frequent stimuli after presentation of an infrequent no-go or stop signal, respectively (Rubia et al., 2007). Stroop, Simon or Erikson flanker interference inhibition tasks measure the ability to inhibit a pre-potent response tendency that conflicts with the primary intended action, while switching measures the ability to inhibit previously valid stimulus-response associations to engage in new ones (Rubia et al., 2007). While in Stop, GNG and interference inhibition tasks, a pre-potent motor response has to be inhibited, switching requires, in addition to motor inhibition, reengagement in a different response. However, all these tasks share inhibitory processes (Hugdahl et al., 2015) which are mediated in adults and children by overlapping inferior and medial fronto-striato-thalamo-parietal networks, including ventrolateral prefrontal cortex (VLPFC)/anterior insula, supplementary motor (SMA), anterior cingulate cortex (ACC), caudate, subthalamic nucleus, and inferior parietal lobe (IPL) (Rubia et al., 2013, Cai et al., 2014, Dambacher et al., 2014, Rae et al., 2014, Hugdahl et al., 2015). Both OCD (Rubia et al., 2011, Dickstein et al., 2013, van Velzen et al., 2014) and ASD (Chantiluke et al., 2015b, Chmielewski and Beste, 2015, Eng et al., 2015) have deficits in performance and fronto-striato-parietal activation during these inhibitory control tasks, suggesting that impaired inhibition could be a trans-diagnostic behavioural phenotype.

In ASD, functional magnetic resonance imaging (fMRI) studies of motor/cognitive interference inhibition and switching report abnormalities in fronto-striato-parietal areas including DLPFC and VLPFC (Duerden et al., 2013, Daly et al., 2014, Chantiluke et al., 2015b, Shafritz et al., 2015), r/dACC/MPFC (Vaidya et al.,

2011, Fan et al., 2012), insula (Schmitz et al., 2006, Kana et al., 2007, Shafritz et al., 2015), parietal regions (Solomon et al., 2014, Chantiluke et al., 2015b) and caudate (Vaidya et al., 2011, Daly et al., 2014), as also shown in meta-analyses of non-social processes that included inhibitory control tasks (Di Martino et al., 2009, Philip et al., 2012, Dickstein et al., 2013). Structural meta-analyses of GMV in ASD implicate fronto-limbic and fronto-parietal abnormalities, reporting decreased GMV in cerebellar, hippocampal, amygdala and parietal regions but increased GMV in superior frontal, striatal and temporal regions (Via et al., 2011, Nickl-Jockschat et al., 2012, DeRamus and Kana, 2015), with basal ganglia (BG) abnormalities associated with symptom severity (Wolff et al., 2013).

FMRI studies of response/interference inhibition and switching in children and adults with OCD have consistently shown hypoactivation in rostral and dorsal ACC and medial prefrontal cortex (r/dACC/MPFC), VLPFC and dorsolateral prefrontal cortex (DLPFC) as well as altered striatal activation (Rubia et al., 2010a, Rubia et al., 2011), supported by a recent meta-analysis and review (van Velzen et al., 2014, Eng et al., 2015). Structural meta- and mega-analyses of whole-brain voxel-based morphometry (VBM) studies in OCD report decreased grey matter volumes (GMV) in r/dACC/MPFC and ventromedial orbitofrontal cortex (vmOFC) but increased GMV in bilateral striatum (Radua et al., 2010, Peng et al., 2012, deWit et al., 2014, Eng et al., 2015), which furthermore has been linked to poor inhibitory performance, suggesting fronto-striatal dysregulation (Menzies et al., 2007).

Despite apparent overlap in frontal and striatal abnormalities between the two disorders, no neuroimaging studies have directly compared ASD and OCD patients. Given the similarities in clinical phenotypes between these disorders (Robbins et al.,

2012), establishing common and distinct neuroanatomical and neurofunctional biomarkers may help with future differential diagnosis and treatment development.

The aim of this study was therefore to investigate whether a common behavioural phenotype may be underpinned by common and/or distinct neural signatures in the two disorders. For this purpose, we conducted a quantitative meta-analysis comparing OCD and ASD in brain function/structure abnormalities using whole-brain VBM and fMRI studies of inhibitory control, and compared multimodal structural and functional neural abnormalities.

We hypothesized that OCD patients would show disorder-specific fronto-striatal dysregulation, i.e. increased BG but decreased ventromedial and r/dACC/MPFC GMV activation (Radua et al., 2010, van Velzen et al., 2014), while ASD patients would show disorder-specific reductions in lateral fronto-striato-limbic volumes and activations (Via et al., 2011, DeRamus and Kana, 2015). We further predicted shared underactivation and reduced structure in medial prefrontal regions (Vaidya et al., 2011, Fan et al., 2012, Eng et al., 2015).

4.2 Methods and materials

4.2.1 Study selection

A comprehensive literature search was conducted by CC, SL and LN through December 2015 for whole-brain imaging studies using VBM or fMRI of inhibitory control in paediatric and adult ASD and OCD (using stop, go/no-go, Simon, Stroop, Eriksen Flanker or switching tasks). For details and search terms see Supplementary Information, section 4.6 of this thesis. Studies meeting the following criteria were included: (1) comparison with a control group (2) for fMRI, use of a task investigating

inhibitory control (see above), (3) included minimum 10 patients, (4) used standardised measures to assess OCD or ASD, (5) reported sufficient information to calculate effect-sizes (i.e. software/coordinates for relevant contrasts) and (6) within one study, used the same significance/extent threshold throughout the whole brain in all analyses. Authors were contacted for additional information if necessary. Studies were excluded if they (1) used region-of-interest (ROI) approaches, (2) did not perform statistical comparisons between cases and controls and (3) did not report peak coordinates for relevant contrasts. ROI approaches may be more appropriate than whole-brain investigations when researchers are interested in the activation of a specific brain region. However, ROI studies were excluded from this meta-analysis because when conducting a *voxel-wise whole-brain* meta-analysis, inclusion of ROI analyses would bias the results, as voxels within ROIs would be set to have the effect-sizes reported in the papers whereas the voxels in the rest of the brain would be *unfairly* set to have no effect-size. The exclusion of ROI studies is therefore recommended practice in structural and functional MRI whole-brain meta-analyses (Radua and Mataix-Cols, 2009, Radua et al., 2010, Nakao et al., 2011, Via et al., 2011, Hart et al., 2012, Ersche et al., 2013, Hart et al., 2013, Gabay et al., 2014, Lim et al., 2014, Radua et al., 2014a, Radua et al., 2014b, Rubia et al., 2014, Norman et al., 2016). MOOSE guidelines for meta-analyses of observational studies were followed (Stroup et al., 2000). To avoid duplication, conjunctive group differences across tasks/conditions or main group effects across task conditions were excluded. Peak coordinates and effect-sizes of significant activation differences between patients and controls (or statistical maps where possible) were extracted from contrasts of interest for each study.

4.2.2 Statistical methods

Meta-analyses of regional differences in activation or GMV were conducted using voxel-wise anisotropic effect-size Seed-based *d* Mapping (AES-SDM; http://www.sdmproject.com). Methods employed by SDM are described elsewhere (Radua and Mataix-Cols, 2009, Radua et al., 2014c) and summarized briefly here. SDM uses reported peak coordinates and effect-sizes from each study to recreate effect-size maps and an effect-size variance map of the signed (positive/negative) GMV or activation differences between patients and controls, converting the *t*-value of each peak to Hedges effect-size and applying an anisotropic non-normalized Gaussian kernel so voxels more correlated with the peak have higher effect-sizes. All maps were combined with a standard random-effects model, accounting for sample size, intra-study variability and between-study heterogeneity (Radua et al., 2012). Statistical significance was determined by permutation tests and default thresholds (Radua et al., 2014c).

Some studies included different fMRI tasks in identical or largely overlapping samples (Schmitz et al., 2006, Woolley et al., 2008, Page et al., 2009, Morein-Zamir et al., 2015), or compared patient subgroups to the same controls (Subirà et al., 2013, Hashimoto et al., 2014). To address this, SDM was modified to allow calculation of a single, combined map with reduced variance for such studies to avoid dependent data in analyses (see Supplementary Information, section 4.6 of this thesis).

Separate analyses within each patient group were first performed to examine GMV and activation differences compared to their respective controls. Then, a quantitative comparison of abnormalities in GMV and activation between ASD and OCD relative to controls was conducted by calculating the difference between each patient group across each voxel and using randomization tests to establish significance.

Meta-regressions were conducted within the OCD group (Radua and Mataix-Cols, 2009) to examine effects of antidepressants on GMV and fMRI abnormalities. Most ASD patients were not receiving medication or insufficient information was provided.

Areas of shared abnormalities between patient groups versus controls within each modality were determined in conjunction analyses by computing *p*-value overlap within each voxel from the original meta-analytic maps accounting for error (Radua et al., 2013). This method was similarly used to perform multimodal analyses showing overlapping functional and structural abnormalities within each patient group relative to controls. Conjunction analysis determined overlapping (or distinct) regions between patient groups across both modalities.

The inclusion of several paradigms to assess inhibitory control introduces task-related heterogeneity. Given that there were not sufficient studies (minimum 10 studies recommended for SDM meta-analyses (Radua and Mataix-Cols, 2009)) to conduct subgroup analyses by task-type, a supplementary meta-analysis was performed covarying for task-type (response/interference inhibition, switching).

Default SDM thresholds were used (voxel $p<.005$; peak height $z=1$;cluster extent=10 voxels); a threshold of $p<.0005$ was used for meta-regressions, and only regions found in the main between-group analysis were included (Radua and Mataix-Cols, 2009, Radua et al., 2012). Jackknife sensitivity analyses were conducted to establish reproducibility of results by iteratively repeating analyses, excluding one dataset each time (Radua and Mataix-Cols, 2009). Funnel plots and Egger's tests were conducted to detect abnormalities in results, e.g. conflicting studies or publication bias.

4.3 Results

4.3.1 Included studies

Included were 32 VBM studies comparing ASD individuals to controls (ASD=911; Controls=932), 30 VBM studies comparing OCD patients to controls (OCD=928; Controls=942), 12 inhibitory control fMRI studies comparing ASD patients to controls (ASD=188; Controls=196) and 14 fMRI studies comparing OCD patients to controls (OCD=247; Controls=244) (Table 4.1 and Supplementary Information, section 4.6).

TABLE 4.1 DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF INCLUDED STUDIES

(A) Demographic and clinical characteristics of the 32 ASD VBM datasets

		Patients			Controls			Brain regions of GMV differences	
Source	Adult/ child	N (% male)	Mean age, y	Age range	N (% male)	Mean age, y	Age range	Patients>HC	HC>Patients
(Abell et al., 1999)	adult	15 (80)	28.8	--	15 (80)	25.3	--	L amygdala, R & L cerebellum, vermis, L middle temporal gyrus, R inf. temporal gyrus	R paracingulate gyrus, L IFG, L occipito-temporal junction
(McAlonan et al., 2002)	adult	21 (90)	32	18-49	24 (92)	33	18-49	-	R cerebellum, R & L lenticular nucleus, R cingulate gyrus, R precuneus, R & L medial frontal gyrus, R sup. frontal gyrus
(Boddaert et al., 2004)	child	21 (76)	9.3	7-15	12 (58)	10.8	7-15	-	R & L sup. temporal sulcus

(Waiter et al., 2004)	child	16 (100)	15.4	12-20	16 (100)	15.5	12-20	L sup. frontal gyrus, R fusiform gyrus, R medial frontal gyrus, L middle temporal gyrus, R PCC, R & L sup. temporal gyrus, L lingual gyrus, L IFG, L middle frontal gyrus, L inf. occipital gyrus, L parahippocampal gyrus	R thalamus
(Kwon et al., 2004)	child	20 (100)	13.5	10-18	13 (100)	13.6	10-18	-	R inf. temporal gyrus/entorhinal cortex
(Rojas et al., 2006)	adult	24 (100)	20.79	7-44	23 (100)	21.4	7-44	-	-
(Schmitz et al., 2006)	adult	10 (100)	38	18-52	12 (100)	39	18-52	L IFG, ACC, R sup. frontal gyrus, R & L middle frontal gyrus	-
(Brieber et al., 2007)	child	15 (100)	14.2	10-16	15 (100)	13.3	10-16	R supramarginal gyrus, L postcentral gyrus	R & L inf. temporal gyrus/hippocampus-amygdala complex, L middle occipital gyrus, L premotor, L hippocampus

(Craig et al., 2007)	adult	14 (0)	37.9	--	19 (0)	35	--	-	L cuneus, L sup./inf. temporal gyrus, R middle temporal gyrus, R ACC
(Bonilha et al., 2008)	child	12 (100)	12.4	8-15	16 (100)	13.2	--	R & L IFG, cuneus, cingulate, claustrum, precuneus, thalamus, sup./medial frontal, sup. parietal, sup./inf./middle temporal gyrus, insula, putamen, ACC, fusiform, middle/inf. occipital, lingual gyrus, precentral gyrus, parahippocampal gyrus, cerebellum, R caudate	-
(Freitag et al., 2008)	child	15 (87)	17.5	--	15 (87)	18.6	--	-	R intraparietal sulcus
(Ke et al., 2008)	child	17 (82)	8.9	6-14	15 (80)	9.73	6-14	R & L supramarginal gyrus, R postcentral, R medial frontal gyrus, R cerebellum	R parahippocampal gyrus

(McAlonan et al., 2008)	child	33 (82)	11.6	7-16	55 (86)	10.7	7-16	-	Cerebellum, L striatum/ globus pallidus, R caudate, R putamen/globus pallidus, L sup. temporal gyrus, L prefrontal/insula, R mPFC, L pre/postcentral, R precuneus
(Langen et al., 2009)	child	99 (92)	12.89	7-24	89 (92)	12.4	6-24	-	-
(Wilson et al., 2009)	adult	10 (80)	30.1	22-47	10 (70)	29.4	21-43	-	-
(Toal et al., 2010)	adult	65 (88)	31	16-59	33 (91)	32	19-58	-	R & L cerebellum/parahippocampal gyrus/fusiform, R inf. temporal gyrus
(Hyde et al., 2010)	adult	15 (100)	22.7	14-33	13 (100)	19.2	14-34	Brainstem, R medial frontal gyrus, L medial OFG, R & L middle frontal gyrus	R postcentral, R & L precentral gyrus
(Kosaka et al., 2010)	adult	32 (100)	23.8	17-32	40 (100)	22.5	18-34	-	R insula, R IFG, R inf. parietal

(Mengotti et al., 2011)	child	20 (90)	7	4-14	22 (91)	7.7	4-11	R inf. parietal, R sup. occipital, R & L inf. temporal gyrus, L sup. parietal lobule, L precuneus	R IFG, L SMA
(Riva et al., 2011)	child	21 (62)	6.5	3-10	21 (62)	6.8	3-10	-	Nucleus accumbens, SMA, R & L insula/putamen, R & L cerebellum, L DLPFC, L inf./sup./middle temporal gyrus, L precuneus, L IFG, L occipito-basal cortex, R postcentral/IPL
(Groen et al., 2011)	child	17 (82)	14.4	12-18	25 (88)	15.5	12-18	-	-
(Kurth et al., 2011)	child	52 (73)	11.2	5-20	52 (73)	11.1	6-19	-	Hypothalamus
(Poustka et al., 2012)	child	18 (89)	9.7	6-12	18 (89)	9.7	6-12	-	-
(Calderoni et al., 2012)	child	38 (0)	4.4	2-8	38 (0)	4.4	2-8	L sup. frontal gyrus	-

(Ecker et al., 2012)	adult	89 (100)	27	18-43	89 (100)	28	18-43	R & L inf./sup./middle temporal gyrus, R & L fusiform, R & L parahippocampal, R & L insula, L IFG, L putamen, L caudate, L thalamus, R & L middle frontal gyrus, R & L pre/postcentral, R IPL	R inf./middle temporal gyrus, R cerebellum, R fusiform, R lingual gyrus, R & L inf. occipital, R cuneus/precuneus, R PCC, R sup. occipital
(Greimel et al., 2013)	adult	51 (100)	18.3	10-50	47 (100)	21.4	8-47	-	ACC, R & L posterior STS, R middle temporal gyrus
(Mueller et al., 2013)	adult	12 (75)	35.5	--	12 (67)	33.3	--	-	R & L sup. parietal/supramarginal gyrus, R & L medial temporal gyrus, R & L IFG/OFC, L middle frontal gyrus, L frontal pole, R & L mPFC, L insula
(Poulin-Lord et al., 2014)	adult	23 (87)	19.8	14-30	22 (86)	22.6	15-35	-	-
(Lim et al., 2015)	child	19 (100)	14.9	11-17	33 (100)	14.9	11-17	L middle/sup. temporal gyrus, L medial frontal gyrus	-

(Gori et al., 2015)	child	21 (100)	4.17	34-70	20 (100)	4	24-70	-	-
(Itahashi et al., 2015)	adult	46 (100)	30.2	19-50	46 (100)	30.5	19-47	-	-
(Foster et al., 2015)	child	38 (100)	12.4	6-17	46 (100)	12.6	7-17	R central sulcus, L medial frontal gyrus, R & L IFG, R & L precentral, L middle frontal gyrus, L pre-SMA, R sup. frontal sulcus & gyrus, L ACC, L OFC, L inf. & sup. temporal gyrus, R & L middle temporal gyrus, L Heschel's gyrus, R lingual gyrus, L fusiform gyrus, L postcentral, L PCC, L precuneus, R supramarginal/ angular gyrus, L inf. occipital, R & L cuneus, L putamen, L caudate	R sup. temporal gyrus, R & L supramarginal gyrus, L cerebellum

(B) Demographic and clinical characteristics of the 30 OCD VBM datasets

Source	Adult/ child	Patients				Controls			Brain regions of GMV differences	
		N (% male)	Mean age, y	Age range	SSRI use	N (% male)	Mean age, y	Age range	Patients>HC	HC>Patients
(Pujol et al., 2004)	adult	72 (56)	29.8	18-60	54 med., 13 prev. med., 2 naïve	72 (56)	30.1	8-57	R ventral putamen, L anterior cerebellum, L ventral putamen	R medial frontal gyrus, L gyrus rectus, L posterior insula
(Riffkin et al., 2005)	adult	18 (44)	36.1	28-65	3 med., 15 unmed.	18 (44)	34.6	19-54	-	-
(Valente Jr et al., 2005)	adult	19 (53)	32.7	--	16 med., 3 naïve	15 (47)	32.3	--	L posterior OFC/AI, L & R parahippocampal/ fusiform gyri	L ACC/medial frontal gyri, R angular/ supramarginal gyri
(Carmona et al., 2007)	child	18 (72)	12.9	--	10 med., 8 naïve	18 (72)	13	--	-	R & L frontal mid, R & L frontal inf. tri., R frontal inf. oper., R frontal sp., L rolandic operculum, R & L cingulate, R & L precuneus

(Soriano-Mas et al., 2007)	adult	30 (70)	31.9	18-63	26 med., 2 prev. med., 2 naïve	30 (100)	31.8	18-63	-	-
(Yoo et al., 2008)	adult	71 (66)	26.6	--	71 med.	71 (66)	26.7	--	R & L postcentral gyrus, R thalamus, L putamen	R cingulate gyrus, R & L IFG, R medial frontal gyrus, R & L insula, L sup. temporal gyrus, R supramarginal gyrus, R precentral gyrus, L middle frontal gyrus
(Gilbert et al., 2008a)	child	10 (60)	12.9	8-16	0 med., 10 naïve	10 (60)	13.4	9-17	-	L anterior cingulate, R & L medial sup. frontal gyrus
(Szeszko et al., 2008)	child	37 (38)	13	--	0 med., 37 naïve	26 (35)	13	--	R & L putamen, R & L OFC, R sup. temporal, R frontal pole, R & L parietal	R & L occipital
(Christian et al., 2008)	adult	21 (71)	38	--	17 med., 4 unmed.	21 (71)	38.9	--	L thalamus	-
(Gilbert et al., 2008b)	adult	25 (52)	37.5	27-62	20 med., 5 unmed.	20 (45)	29.8	19-51	R & L midbrain	R & L BA 9, 6, 46, R BA 8

(Kopřivová et al., 2009)	adult	14 (36)	28.6	--	10 med., 13 prev. med., 1 naïve	15 (40)	28.7	--	-	R lingual gyrus, R & L medial/sup. frontal gyrus, ACC, R sup. occipital gyrus, R inf. parietal lobule, R sup. temporal gyrus, L middle temporal gyrus, R precentral gyrus, pons/ mesencephalon, R fusiform gyrus, L cerebellum
(van den Heuvel et al., 2009)	adult	55 (29)	33.7	19-54	0 med., 30 prev. med., 25 naïve	50 (40)	31.4	21-53	-	L lateral OFC, L DLPFC, L IFC, R & L mPFC
(Matsumoto et al., 2010)	adult	16 (44)	32.8	--	6 med., 6 prev med., 4 naïve	31 (44)	32.6	--	-	R dorsal PCC, L caudal PCC
(Britton et al., 2010)	child	15 (60)	13.5	10-17	15 med., 0 naïve	20 (65)	13.6	10-17	Medial frontal gyrus, OFC, R ACC, IFG	-

(Togao et al., 2010)	adult	23 (46)	32.6	21-56	18 med., 5 naïve	26 (46)	34.6	21-48	-	R & L medial PFC, R OFC, R DLPFC, R middle temporal gyrus/middle occipital gyrus, L middle occipital gyrus
(Lázaro et al., 2011)	child	27 (56)	15.6	--	27 med., 0 naïve	27 (48)	16.1	--	-	-
(Zarei et al., 2011)	child	26 (54)	16.6	12-18	16 med., 10 naïve	26 (54)	16.5	12-18	R & L caudate nuclei, R posterior putamen, R globus pallidus	-
(Exner et al., 2012)	adult	23 (39)	31.3	--	13 med., 10 unmed.	36 (39)	30.4	--	L temporoparietal/ superior temporal lobe	dorsal mediofrontal cortex
(Hoexter et al., 2013)	adult	38 (40)	31.5	--	0 med., 38 naïve	36 (36)	27.8	--	PCC, R IFG, L postcentral gyrus/cortex	L & R DLPFC, L mid/sup. occipital, R IPL, R inf. temporal
(Huyser et al., 2013)	child	29 (38)	13.8	9-18	0 med., 2 prev. med., 27 naïve	29 (38)	13.6	9-18	L insula/frontal pole, L sup. parietal, L supramarginal gyrus	-
(Hou et al., 2013)	adult	33 (55)	25.3	--	0 med., 33 naïve	33 (55)	25	--	L caudate, L thalamus, PCC	R & L medial OFC, L ACC, L IFG

(Tan et al., 2013)	adult	28 (68)	25.4	--	0 med., 18 prev. med., 10 naïve	22 (68)	27.9	--	R & L middle temporal gyri, R & L middle occipital gyri, R & L globus pallidus, R inf. parietal gyrus, L sup. parietal gyrus, R parahippocampus, R supramarginal gyrus, R medial sup. frontal gyrus, L inf. frontal opercular gyrus	-
(Subirà et al., 2013)	adult	95 (56)	33.4	--	95 med., 0 naïve	95 (58)	33.9	--	R & L putamen	L anterior temporal lobe
(Tang et al., 2013)	adult	18 (61)	25.5	--	0 med., 18 prev. med.	26 (58)	25.2	--	L putamen	L PCC, L mediodorsal thalamus
(Hashimoto et al., 2014)	adult	39 (46)	34.1	--	39 med., 0 naïve	30 (47)	32.5	--	-	R thalamus, R caudate, L PCC, L DLPFC
(Spalletta et al., 2014)	adult	20 (60)	33.1	--	11 med., 7 prev. med., 2 naïve	20 (60)	35.2	--	-	-

(Okada et al., 2015)	adult	37 (38)	34.4	22-58	32 med., 3 prev. med., 2 naïve	37 (38)	36.8	22-60	L precentral gyrus	R middle temporal gyrus, L DLPFC, R PCC, R OFC, R supramarginal gyrus, L IFG
(Kim et al., 2015b)	adult	30 (67)	25	--	0 med., 8 prev. med., 22 naïve	34 (68)	23.9	--	-	-
(Tang et al., 2015)	adult	26 (58)	25.5	--	0 med., 26 naïve	32 (53)	26.2	--	L insula, R parahippocampal gyrus	R DLPFC, L sup. temporal gyrus, L precuneus, R precentral
(Jayarajan et al., 2015)	child	15 (53)	14.1	--	13 med., 2 naïve	15 (53)	14.3	--	-	-

(C) Demographic and clinical characteristics of the 12 ASD fMRI datasets

			Patients			Controls			Brain regions of activation differences	
Source	Adult/ child	Task	N (% male)	Mean age, y	Age rang e	N (% male)	Mean age, y	Age range	Patients>HC	HC>Patients
(Schmitz et al., 2006)	adult	GNG Switch Stroop	10 (100)	38	18-52	12 (100)	39	18-52	GNG: L mid/IFG, L OFC; Stroop: L insula; Switch: R IPL, L mesial parietal	-
(Kennedy et al., 2006)	adult	Stroop	15 (100)	25.5	16-44	14 (100)	26.1	--	R supramarginal gyrus, R precuneus, R & L IPL, R sup. frontal gyrus, L ACC	-
(Kana et al., 2007)	adult	GNG	12 (92)	26.8	--	12 (92)	22.5	--	-	L inf. temporal gyrus, R parahippocampal gyrus, R calcarine sulcus, R premotor, R middle cingulate, R & L postcentral, R insula/IFG, L lingual gyrus

(Shafritz et al., 2008)	adult	Switch	18 (89)	22.3	--	15 (87)	24.3	--	-	DLPFC, ACC, inf. parietal sulcus, L insula
(Vaidya et al., 2011)	child	Stroop	15 (100)	10.8	7-12	18 (100)	11.0	--	-	ACC, L middle frontal gyrus, R caudate
(Fan et al., 2012)	adult	Flanker	12 (75)	30	--	12 (83)	28	--	-	ACC
(Duerden et al., 2013)	adult	GNG	13 (69)	25.9	19-39	17 (71)	29	20-43	R IFG, R fusiform gyrus	R middle frontal gyrus
(Solomon et al., 2014)	child	POP	27 (19)	15.4	12-18	27 (19)	16.1	12-18	-	L PCC, L lingual gyrus, L middle occipital
(Chantiluke et al., 2015b)	child	Stop	19 (100)	14.7	10-17	25 (100)	13.4	10-17	R & L IFG	L IPL
(Ambrosino et al., 2014)	child	GNG	19 (100)	11.5	9-12	19 (100)	11.1	9-14	-	-

(Daly et al., 2014)	adult	GNG	14 (100)	31	--	14 (100)	31	--	R caudate, R cerebellum	R IFC, L thalamus
(Shafritz et al., 2015)	adult	GNG	15 (80)	18.1	13-23	15 (80)	18.4	12-23	-	R VLPFC/insula

(D) Demographic and clinical characteristics of the 14 OCD fMRI datasets

			Patients				Controls			Brain regions of activation differences	
Source	Adult/ child	Task	N (% male)	Mean age, y	Age range	SSRI use	N (% male)	Mean age, y	Age range	Patients>HC	HC>Patients
(Nakao et al., 2005)	adult	Stroop	24 (38)	33.9	21-54	0 med., 24 unmed.	14 (36)	30.2	24-43	R frontal cortex	ACC, R caudate, R & L temporal cortex, R brainstem
(Roth et al., 2007)	adult	GNG	12 (43)	37.8	--	6 med., 6 unmed.	14 (42)	34.9	--	R & L postcentral, R cuneus, L supramarginal gyrus	R IFG, R medial/sup. frontal gyrus, R fusiform, R middle temporal gyrus, R thalamus
(Yücel et al., 2007)	adult	MSIT	19 (53)	33.7	--	11 med., 8 unmed.	19 (53)	30.6	--	SMA, L sup. parietal, L precentral, R middle frontal gyrus, L IFG, L putamen	Rostral ACC, L IFG, R fusiform gyrus

(Gu et al., 2008)	adult	Switch	21 (86)	23.6	--	11 med., 2 prev. med., 8 naïve	21 (86)	24.8	--	-	R DLPFC, R & L premotor, L VLPFC, R OFC, R & L medial frontal cortex, ACC, R & L PCC, R uncus, R insula, R & L parietal, R middle/sup. temporal gyrus, R & L occipital, R & L caudate
(Woolley et al., 2008)	child	Stop Stroop Switch	10 (100)	14.3	12-16	8 med., 2 unmed.	9 (100)	14.5	12-16	-	Stop: R & L OFC, R thalamus/BG; Stroop: R & L cerebellum, R mid. temporal gyrus; Switch: R & L IPL/sup. temp, R & L cerebellum

(Page et al., 2009)	adult	GNG Stroop Switch	10 (100)	39.1	--	0 med., 4 prev. med., 6 naïve	11 (100)	34.1	--	GNG: R & L PCC/middle temporal gyrus, L cerebellum, R vmPFC, R middle/ sup. temporal gyrus, R premotor; Stroop: L cerebellum/PCC; Switch: -	GNG: L cerebellum, R & L vmOFC/ACC, R BG/thalamus/ hippocampus; Stroop: R mid/sup. temp. gyrus, L IPL/sup. temp, L sup. parietal/ precuneus; Switch: L DLPFC/ACC, L precuneus/PCC
(Fitzgerald et al., 2010)	child	MSIT	18 (33)	13.9	8-18	12 med., 6 naïve	18 (33)	14.1	8-18	-	-
(Britton et al., 2010)	child	Set-shift	15 (60)	13.5	10-17	15 med.	20 (65)	13.6	10-17	-	-
(Schlösser et al., 2010)	adult	Stroop	21 (24)	31.3	--	2 med., 10 unmed., 9 naïve	21 (24)	28.8	--	R & L DLPFC	L occipital lobe

(Huyser et al., 2011)	child	Flanker	25 (36)	14.0	9-19	0 med., 1 prev. med., 24 naïve	25 (36)	13.7	8-19	-	-
(Pena-Garijo et al., 2011)	adult	GNG	13 (39)	37.1	--	8 med., 5 unmed.	13 (46)	37.1	--	R occipital, L IPL, L cerebellum	L ACC, R caudate, dmPFC
(Kang et al., 2013)	adult	Stop	18 (66)	24.9	--	0 med., 6 prev. med., 12 naïve	18 (66)	24.7	--	R & L sup. parietal, L cerebellum, R parahippocampal cortex	L precentral, R fusiform, L middle temporal, R middle occipital, R sup. temporal, L angular cortex, R putamen, R & L caudate, R ACC, R calcarine, R middle cingulate, L cerebellum
(Marsh et al., 2014)	adult	Stroop	22 (50)	30	--	0 med., 8 prev. med., 14 naïve	22 (50)	30.1	--	-	ACC, R & L sup. frontal gyrus, R & L middle frontal gyrus

(Morein-Zamir et al., 2015)	adult	Switch GNG	19 (74)	37.8	--	14 med., 5 unmed.	19 (74)	36.2	--	Switch: - ; GNG: L cuneus, R precentral gyrus, L caudate	Switch: L & R fusiform, R middle temporal, L & R middle occipital, L lingual, L SMA & pre-SMA, R thalamus, L middle frontal, R precuneus; GNG: -

Abbreviations: %, percentage; ACC, anterior cingulate cortex; ASD, autism spectrum disorders; DLPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; fmri, functional magnetic resonance imaging; GNG, go/no-go; IFG, inferior frontal gyrus; inf., inferior; L, left; med., medicated; MSIT, multisource interference task; mid, middle; OCD, obsessive compulsive disorder; PCC, posterior cingulate cortex; POP, preparing to overcome prepotency; prev. R, right; SMA, supplementary motor area; SSRI, selective serotonin reuptake inhibitor; STS, superior temporal sulcus; sup., superior; temp., temporal; unmed. unmedicated (at time of scan); VLPFC, ventrolateral prefrontal cortex; vmOFC, ventromedial orbitofrontal cortex; VBM, voxel-based morphometry; y, years

4.3.2 Group differences in demographics

Across all studies, patients were age and sex-matched to controls. Compared to OCD, ASD VBM [patients: $F(1,61)=42$, $p<0.001$; controls: $F(1,61)=37$, $p<0.001$] and fMRI studies [patients: $F(1,25)=18$, $p<0.001$; controls: $F(1,25)=19$, $p<0.001$] included more males. In the VBM meta-analysis, ASD patients were younger than OCD patients [$F(1,61)=19$, $p<0.001$] (corresponding controls [$F(1,61)=21$, $p<0.001$]). Across fMRI studies, patients [$F(1,18)=0.1$, $p=0.71$] and controls [$F(1,16)=0.3$, $p=0.56$] were matched on IQ, but too few VBM studies reported IQ scores to include this analysis (Table 4.2A).

To ensure group differences were not due to sex/age differences, comparative VBM and fMRI meta-analyses were covaried with sex, and only the comparative VBM meta-analysis was additionally covaried with age (as groups were age-matched in the fMRI comparison). In addition, the comparative meta-analyses were repeated on age and sex-matched subgroups (Table 4.2B). In this analysis, group-differences were minimized to the point of losing significance (p-values>0.5; any mild effect would reach significance given the size of the overall samples) (see Supplementary Information, section 4.6).

Last, the proportion of fMRI studies which showed significant performance differences between patients and controls (ASD: 4/12; OCD: 4/14) did not differ between ASD and OCD ($\chi^2=0.07$, $p=0.8$), suggesting that group-differences in performance did not contribute to activation differences.

Table 4.2 Demographic information of meta-analysis samples

(A) Total study sample				
	ASD patients	**OCD patients**	**ASD controls**	**OCD controls**
VBM				
n	911	928	932	942
% males	85	53	84	51
Mean age[a], y (SD)	18.5 (9.1)	27.8 (7.6)	18.1 (9.0)	27.6 (7.3)
Age range	2-70	8-65	2-70	8-63
fMRI				
n	188	247	196	244
% males	88	54	89	55
Mean age[a], y (SD)	21.4 (7.7)	27.1 (8.9)	21.3 (8.3)	25.7 (11.0)
Age range	7-52	8-54	9-52	8-43
Mean IQ[a] (SD)	109.0 (5.5)	108.0 (5.2)	114.9 (5.0)	113.5 (3.6)
(B) Age and sex-matched sub-sample				
	ASD patients	OCD patients	ASD controls	OCD controls
VBM				
n	258	412	295	441
% males	74	58	73	55
Mean age[a], y (SD)	18.0 (11.9)	25 (7.7)	18.6 (11.3)	24.8 (7.2)
Age range	2-52	10-63	2-52	10-63
fMRI				
n	140	127	140	134
% males	84	70	86	70
Mean age[a], y (SD)	22.4 (6.9)	27.0 (9.8)	22.5 (6.8)	25.9 (8.2)
Age range	7-44	10-17	12-43	10-17
Mean IQ[a] (SD)	108.4 (6.7)	109.9 (4.9)	116.2 (4.2)	113.8 (3.6)

[a]weighted averages

NB: age ranges were not available for all studies, above values based on available information; see Table 4.1 for further details

Abbreviations: ASD, autism spectrum disorders; fMRI, functional magnetic resonance imaging; OCD, obsessive compulsive disorder; SD, standard deviation; VBM, voxel-based morphometry; y, years

4.3.3 Regional differences in GMV

4.3.3.1 ASD VBM analysis

ASD patients relative to controls showed reduced GMV in r/dACC/MPFC, right posterior insula and left cerebellum and enhanced GMV in left middle and superior temporal lobe (STL), right IPL/occipital lobe, left middle frontal gyrus (MFG), left and right precentral and right inferior temporal gyri (

Figure 4.1A**;** Table 4.3A).

4.3.3.2 OCD VBM analysis

OCD patients relative to controls showed decreased GMV in v/r/dACC/MPFC, left VLPFC reaching into premotor cortex/insula/STL and in right IPL, left MFG/DLPFC and left VLPFC and increased GMV in bilateral putamen/caudate/nucleus accumbens (NAcc)/pallidum/amygdala/insula and in bilateral cerebellum, left postcentral gyrus and right superior parietal cortex (Figure 4.1B; Table 4.3B). Meta-regression revealed no association between GMV differences and anti-depressant use in patients at $p<0.0005$.

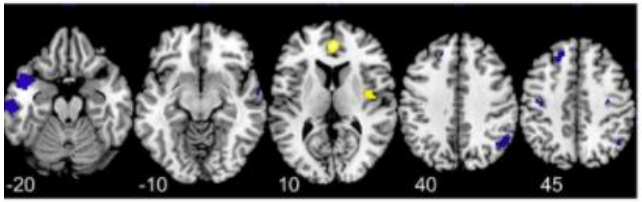
4.3.3.3 Comparison of GMV differences between OCD and ASD

OCD compared to ASD patients (relative to respective control groups) showed larger GMV in bilateral putamen/caudate/NAcc/pallidum/amygdala/insula, extending into right STL, and in left caudate, right inferior temporal gyrus and cuneus but smaller GMV in dACC/MPFC, left superior frontal gyrus and right MFG/premotor cortex (Figure 4.1C; Table 4.3C). Effects in right inferior temporal gyrus, cuneus and right MFG/premotor cortex did not survive the age and sex-matched subgroup meta-analysis (Supplementary Information section 4.6, Figure 4.2C; Table 4.5C).

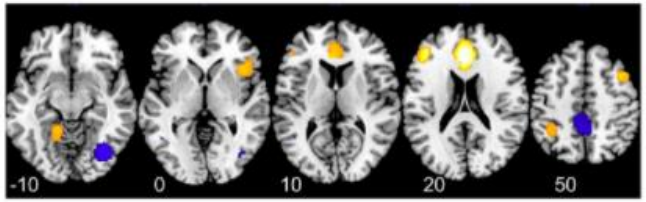
4.3.3.4 GMV conjunction/disjunction analysis

Shared GMV increases were in left ventral striatum (VS)/nucleus accumbens [MNI coord: -20,18,-10; voxels: 390] and shared decreases in r/dACC/MPFC [MNI coord: 4,44,26; voxels: 1843]. Disjunction was seen in right putamen/caudate/insula [MNI coord: 34,-4,4; voxels: 874] where ASD had decreased GMV but OCD had increased GMV and in right IPL [MNI coord: 52,-56,36; voxels: 918], left STL [MNI coord: -44,12,-22; voxels: 634] and left MFG [MNI coord: -20,32,42; voxels: 458] where ASD had increased but OCD decreased GMV (Figure 4.1D). Effects in left VS/nucleus accumbens, right IPL, left STL and left MFG did not survive age and sex-matched subgroup meta-analysis (Figure 4.2D).

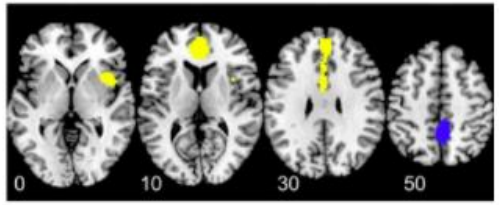
(A) ASD vs. HC VBM



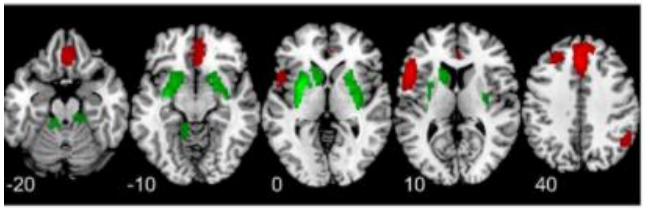
(E) ASD vs. HC fMRI



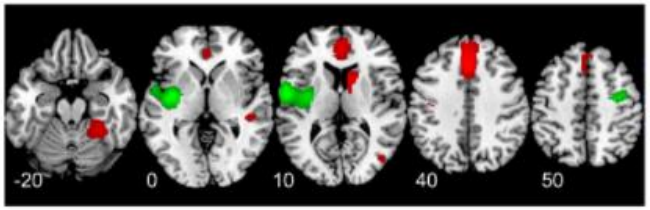
(I) ASD vs. HC multimodal VBM/fMRI



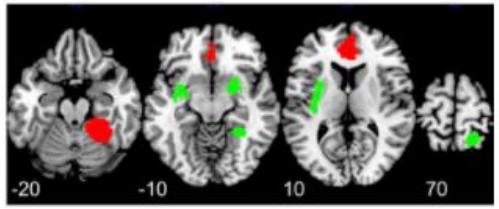
(B) OCD vs. HC VBM



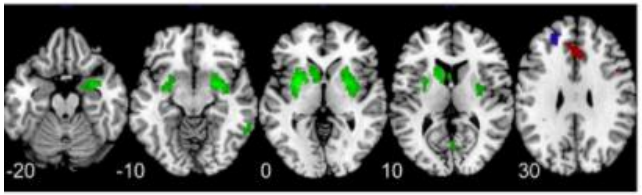
(F) OCD vs. HC fMRI



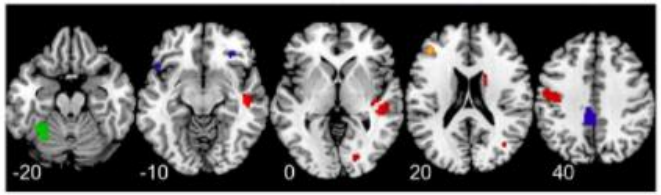
(J) OCD vs. HC multimodal VBM/fMRI



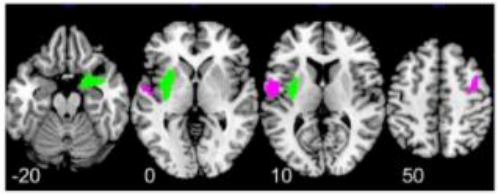
(C) ASD vs. OCD (v. HC) VBM



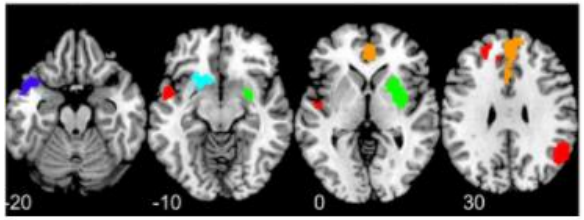
(G) ASD vs. OCD (v. HC) fMRI



(K) ASD vs. OCD (v. HC) multimodal VBM/fMRI



(D) ASD vs. OCD (v. HC) VBM conjunction/disjunction



(H) ASD vs. OCD (v. HC) fMRI conjunction/disjunction

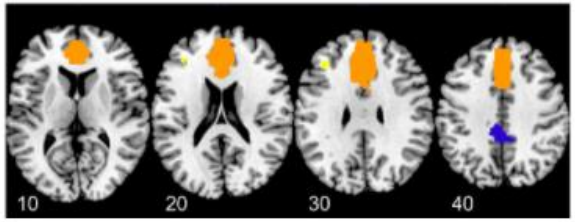


Figure 4.1 Whole-brain meta-analysis of voxel-based morphometry (VBM) and functional magnetic resonance imaging (fMRI) differences among autism spectrum disorder (ASD), obsessive-compulsive disorder (OCD) and control subjects

(A) VBM meta-analysis results for ASD patients relative to controls. **(B)** VBM meta-analysis results for OCD patients relative to controls. **(C)** VBM meta-analysis results for the comparison between ASD patients (vs. controls) and OCD patients (vs. controls). **(D)** VBM meta-analysis results for conjunction/disjunction analysis of ASD and OCD abnormalities (vs. controls). **(E)** fMRI meta-analysis results for ASD patients relative to controls. **(F)** fMRI meta-analysis results for OCD patients relative to controls. **(G)** fMRI meta-analysis results for the comparison between ASD (vs. controls) and OCD (vs. controls). **(H)** fMRI meta-analysis results for conjunction/disjunction analysis of ASD and OCD abnormalities (vs. controls). **(I)** fMRI-VBM multimodal conjunction/disjunction analysis showing overlapping abnormalities in ASD relative to controls. **(J)** fMRI-VBM multimodal conjunction/disjunction analysis showing overlapping abnormalities in OCD relative to controls. **(K)** fMRI-VBM multimodal conjunction/disjunction analysis for the comparison between ASD (vs. controls) and OCD (vs. controls). **Cool colours** (blue in ASD, green in OCD) indicate increased brain structure or function in patients versus controls. **Warm colours** (yellow in ASD, red in OCD) indicate decreased brain structure or function in patients versus controls. For (**D)** and (**H)**, orange and light blue indicate disorder-shared decreases/increases in structure/function, respectively. For (**K)**, **pink** indicates regions that were disjunctive across modalities (i.e. increased in one but decreased in the other) in ASD compared to OCD (vs. controls).

Table 4.3 Meta-analysis results for VBM studies in ASD and OCD

Contrast	Brodmann areas	MNI x,y,z coordinates	SDM z-score	*P* value	No. of voxels
(A) ASD versus HC					
ASD < HC					
r/d ACC/MPFC	32/24/9/10	4,44,16	-1.644	.001	345
R posterior insula	-	44,-12,12	-1.473	.002	65
L cerebellum VIII	-	-10,-66,-48	-1.453	.003	52
ASD > HC					
L middle/sup. temporal lobe	38/21	-44,6,-26	2.436	<.0001	1047
R IPL/occipital lobe	39/19	50,-58,36	1.576	<.001	209
L middle frontal gyrus	8	-20,30,46	1.667	<.001	78
L precentral gyrus	6/4	-38,-14,50	1.482	.002	52
R inf. temporal gyrus	20	60,-4,-14	1.486	.002	49
R precentral gyrus	6/4	34,-16,46	1.353	.003	10
(B) OCD versus HC					
OCD < HC					
v/r/d ACC/MPFC	25/11/24/32/9	-2,30,34	-2.737	<.0001	3199
L VLPFC/premotor cortex/insula/STL	44/45/6/42	-52,18,12	-2.442	<.0001	1095
R IPL	7	52,-56,38	-1.817	<.001	355
L MFG/DLPFC	9	-28,34,38	-1.862	<.001	182
L VLPFC	47	-44,44,-4	-1.466	.004	16

OCD > HC					
L putamen/caudate/NAcc/ pallidum/amygdala/insula	-	-28,4,-2	2.360	<.0001	1582
R putamen/NAcc/ pallidum/amygdala/insula	-	24,4,-2	2.010	<.0001	834
L cerebellum IV/V	-	-14,-40,-20	1.444	<.001	371
R cerebellum IV/V	-	12,-30,-22	1.276	.001	92
L postcentral gyrus	3/1/2	-26,-36,62	1.071	.004	31
R superior parietal gyrus	7	16,-56,72	1.146	.003	23
R cerebellum	-	22,-38,-16	1.053	.004	17
(C) ASD (vs. HC) versus OCD (vs. HC)					
ASD (vs. HC) < OCD (vs. HC)					
R putamen/caudate/NAcc/ pallidum/amygdala/insula/STL	21/38	26,4,-4	-2.307	<.0001	1288
L putamen/caudate/NAcc/ pallidum/amygdala/insula	-	-28,4,-2	-2.375	<.0001	774
L caudate	-	-8,12,2	-2.020	<.001	442
(R inferior temporal lobe)*	37	62,-48,-12	-1.482	.001	95
(R cuneus)*	31	4,-70,10	-1.438	.002	51
ASD (vs. HC) > OCD (vs. HC)					
dACC/MPFC	32/9	-12,40,24	1.390	<.001	304
L superior frontal gyrus	9/8	-22,42,26	1.758	<.0001	121
(R MFG/premotor)*	9/6	40,4,42	1.009	.002	60

Bold indicates regions which survive age and sex-matched subgroup analysis

()* indicates regions which did not survive age and sex-matched subgroup analysis

Abbreviations: ACC, anterior cingulate cortex; ASD, Autism spectrum disorders; BG, basal ganglia; d, dorsal; DLPFC, dorsolateral prefrontal cortex; HC, healthy controls; inf., inferior; IPL, inferior parietal lobe; L, left; MPFC, medial prefrontal cortex; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; NAcc, nucleus accumbens; OCD, obsessive compulsive disorder; R, right; r, rostral; STL, superior temporal lobe; v, ventral; vmOFC, ventromedial orbitofrontal cortex; VLPFC, ventrolateral prefrontal cortex; VBM, voxel-based morphometry

4.3.4 fMRI activation differences in inhibitory control tasks

4.3.4.1 ASD fMRI analysis

ASD patients relative to controls showed decreased activation in r/dACC/MPFC, left DLPFC, right VLPFC/anterior insula, left cerebellum vermis, left IPL and right MFG/premotor cortex. Enhanced activation relative to controls was in precuneus/posterior cingulate cortex (PCC), right inferior temporal/occipital and left middle temporal cortices (Figure 4.1E; Table 4.4A).

4.3.4.2 OCD fMRI analysis

OCD patients relative to controls showed decreased activation in v/r/dACC/MPFC, right caudate, right cerebellum, right STL/middle temporal gyrus, left postcentral gyrus and right PCC. Enhanced activation was observed in left insula/putamen/premotor cortex/ VLPFC/STL, right premotor cortex and left superior parietal cortex (Figure 4.1F; Table 4.4B). Meta-regression with medication status revealed no association between activation differences and anti-depressant use in patients at $p<0.0005$.

4.3.4.3 Comparison of fMRI activation differences between OCD and ASD

Compared to ASD patients, OCD patients had increased activation in left MFG/DLPFC and left cerebellum but reduced activation in right STL/middle temporal lobe, left pre/post-central gyrus/IPL, right and left PCC/precuneus, right and left VLPFC, right caudate, and right occipital lobe (Figure 4.1G; Table 4.4C). Effects in left cerebellum,

right and left VLPFC, right occipital lobe, caudate and left PCC/precuneus did not survive age and sex-matched subgroup meta-analyses (Figure 4.2G; Table 4.6C). Confirmatory analyses including age as covariate confirmed results were not affected by non-significant age differences. Controlling for task-type, the majority of between-patient group-findings remained except disorder-specific underactivation in OCD patients in right STL/middle temporal lobe. Main findings remained when block-design studies which could be confounded by including error trials were excluded.

4.3.4.4 FMRI conjunction/disjunction analysis

Conjunction/disjunction analyses revealed shared underactivation in patient groups relative to controls in r/dACC/MPFC [MNI coord: 0,32,34; voxels: 3732]. Disjunction was seen in PCC/precuneus [MNI coord: -4,-34,46; voxels: 393] where ASD showed increased but OCD decreased activation relative to controls and in left MFG/DLPFC [MNI coord: -36,32,24; voxels: 101], where ASD showed decreased while OCD showed enhanced activation relative to controls (Figure 4.1H). The left MFG/DLPFC cluster did not survive age and sex-matched subgroup meta-analysis (Figure 4.2H).

Table 4.4 Meta-analysis results for fMRI studies of inhibitory control in ASD and OCD

Contrast	Brodmann areas	MNI x,y,z coordinates	SDM *z*-score	*P* value	No. of voxels
(A) ASD versus HC					
ASD < HC					
r/d ACC/MPFC	32/24/9	0,32,22	-1.862	<.0001	2116
L DLPFC	46/9	-44,34,26	-1.821	<.0001	589
R VLPFC/anterior insula	47	44,20,0	-1.466	.001	282
L cerebellum (vermis)	-	-12,-46,-10	-1.418	.001	282
L IPL	40/7	-32,-52,54	-1.378	.002	206
R MFG/premotor cortex	6/8	40,14,50	-1.532	<.001	181
ASD > HC					
Precuneus/PCC	7/5/31/23	-4,-40,54	1.370	<.001	1017
R inf. temporal/occipital lobe	37/19	36,-68,-12	1.534	<.0001	526
L middle temporal gyrus	--	-46,-54,6	1.069	<.001	45
(B) OCD versus HC					
OCD < HC					
v/r/d ACC/MPFC	11/10/9/32/24	-2,26,42	-2.900	<.0001	3717
R caudate	-	14,8,14	-2.408	<.0001	500
R cerebellum	-	30,-46,-16	-2.133	<.001	311
R STL/middle temporal gyrus	21/22	44,-20,-10	-1.893	.001	136
L postcentral gyrus	3/1/2	-40,-16,38	-1.805	.002	30
R PCC	23	16,-38,38	-1.888	.001	17

OCD > HC					
L insula/putamen/premotor cortex/VLPFC/STL	6/44/22	-56,-4,6	1.651	<.0001	1890
R premotor cortex	4/6	36,-8,54	1.257	<.001	321
L superior parietal cortex	7	-18,-62,70	1.034	.001	17
(C) ASD (vs. HC) versus OCD (vs. HC)					
ASD (vs. HC) < OCD (vs. HC)					
L MFG/DLPFC	9/46	-40,34,28	-1.316	<.001	339
(L cerebellum IV)*	-	-30,-50,-22	-1.005	.001	553
ASD (vs. HC) > OCD (vs. HC)					
R STL/middle temporal lobe	21	44,-22,-8	2.394	<.0001	371
L pre/postcentral gyrus/IPL	6/4/3/1/2	-40,-16,40	1.940	<.001	310
R PCC	23	16,-42,36	1.742	.001	22
(PCC/precuneus)*	23/31/7	-4,-42,46	1.719	.001	240
(R VLPFC)*	11/47	30,34,-12	1.761	.001	76
(R occipital lobe/cuneus)*	19/30	20,-82,4	1.753	.001	52
(L VLPFC)*	47/38	-48,22,-8	1.574	.003	42
(R caudate)*	-	18,4,22	1.693	.001	25
(R occipital)*	19	38,-68,20	1.599	.002	22

Bold indicates regions which survived age and sex-matched subgroup analysis

()* indicates regions which did not survive age and sex-matched subgroup analysis

Abbreviations: ACC, anterior cingulate cortex; ASD, Autism spectrum disorders; d, dorsal; DLPFC, dorsolateral prefrontal cortex; HC, healthy controls; inf., inferior; IPL, inferior parietal lobe; L, left; MPFC, medial prefrontal cortex; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; OCD, obsessive compulsive disorder; PCC: posterior cingulate cortex; R, right; r, rostral; STL, superior temporal lobe; v, ventral; vmOFC, ventromedial orbitofrontal cortex; VLPFC, ventrolateral prefrontal cortex; VBM, voxel-based morphometry

4.3.5 Multimodal analyses

4.3.5.1 Multimodal analyses in ASD

Multimodal analyses in ASD showed shared decreases in GMV and activation in dACC/MPFC [MNI coord: 4,44,16; voxels: 1802] and right insula [MNI coord: 40,10,2; voxels: 245]. The precuneus/PCC [MNI coord: 4,-50,48; voxels: 705] was decreased in GMV but increased in activation relative to controls (Figure 4.1I).

4.3.5.2 Multimodal analyses in OCD

Multimodal analyses in OCD showed shared GMV and activation reduction relative to controls in v/r/dACC/MPFC [MNI coord: 6,36,46; voxels: 5126] and shared increases in function and structure in left anterior and posterior insula/putamen [MNI coord: -32,-8,-2; voxels: 932] and right superior parietal gyrus [MNI coord:18,-54,72; voxels: 137]. Left STL/precentral gyrus [MNI coord: -56,2,10; voxels: 1524] was decreased in volume but increased in activation in patients relative to controls while right superior cerebellar hemisphere [MNI coord: 28,-42,-16; voxels: 1034], right anterior insula/putamen [MNI coord: 18,0,-4; voxels: 415] and right caudate [MNI coord: 16,16,4; voxels: 39] were increased in volume but decreased in activation (Figure 4.1J).

4.3.5.3 Multimodal comparison between ASD and OCD

Multimodal comparison between OCD and ASD (vs. controls) showed larger GMV and greater activation in left insula/putamen [MNI coord: -34,-6,4; voxels: 822] were

disorder-specific in OCD versus ASD patients. Enhanced GMV and decreased activation was disorder-specific in ASD relative to OCD in left STL [MNI coord: -58,-2,8; voxels: 394] and right precentral gyrus/premotor cortex [MNI coord: 44,8,44; voxels: 180]. Disorder-specific decreased GMV but increased activation was seen in right amygdala/STL [MNI coord: 24,2,-22; voxels: 500] in ASD relative to OCD (Figure 4.1K). None of the regions that were disorder-specific to ASD survived age and sex-matched subgroup meta-analysis (Figure 4.2K).

4.3.6 Publication bias and robustness analysis

Egger's tests were non-significant (p>0.05, Bonferroni corrected), suggesting there was no evidence of publication bias for the reported clusters. All disorder-specific and disorder-shared findings were robust (Table 4.7-Table 4.14).

4.4 Discussion

This first comparative multimodal meta-analysis of imaging studies of ASD and OCD shows both shared and disorder-specific abnormalities in brain structure and function during inhibitory control. Given group differences in age- and sex-distribution in the included studies, only findings that survived age and sex-matched subgroup meta-analyses are discussed.

Both disorders shared decreased volume and inhibitory activation in r/dACC/MPFC relative to controls. The most prominent disorder-specific finding was in left putamen and

anterior and posterior insula where OCD patients had increased structure *and* inhibitory function compared to controls and ASD patients, while for the VBM meta-analysis, right putamen and insula which were increased in volume in OCD but decreased in ASD patients relative to controls.

Other disorder-differentiated structural abnormalities were in left superior frontal gyrus, which was reduced in volume in OCD patients relative to controls and ASD patients where it was enhanced relative to controls. For fMRI, disorder-specific effects were in left DLPFC, which was reduced, and PCC/precuneus, which was enhanced in function in ASD relative to OCD patients and controls. OCD patients had right superior temporal and inferior parietal underfunctioning relative to ASD patients and controls.

Rostral and dorsal ACC and MPFC are closely interconnected and together play a key role in top-down control of affect and motivation due to close connections with striato-limbic regions (Goodkind et al., 2015). While the vACC/MPFC is associated with affect control (Shenhav et al., 2013, Buhle et al., 2014), more dorsal parts, in particular dACC, are crucial for inhibitory control (Levy and Wagner, 2011, Swick et al., 2011, Cai et al., 2014, Rae et al., 2014) as well as for controlling affective VMPFC-limbic systems (Etkin et al., 2011). The shared r/dACC/MPFC underactivation and reduced GMV may therefore reflect shared deficits in top-down inhibitory control over striato-limbic regions mediating motivation and affect. This finding extends previous meta-analyses in OCD patients showing GMV and inhibitory function in ACC/MPFC (Radua and Mataix-Cols, 2009, Radua et al., 2010, Peng et al., 2012, Eng et al., 2015, Goodkind et al., 2015) relative to

controls, as well as smaller structure/function in these regions in ASD patients (Di Martino et al., 2009, Ha et al., 2015), by showing that this multimodal MPFC dysfunction and dysmorphology is a shared phenotype which may reflect common problems with top-down cognitive and affect control which, furthermore, may be shared with a range of other affective disorders (Goodkind et al., 2015).

The disorder-specific finding of enhanced left striatal and insular function and structure in OCD relative to ASD patients together with reduced v/r/dACC/MPFC GMV and activation extends previous meta-analyses showing increased GMV in right insula (Eng et al., 2015) and left (Radua and Mataix-Cols, 2009, Radua et al., 2010, Peng et al., 2012, Eng et al., 2015) and right BG in OCD by showing that this is disorder-specific relative to ASD. They also extend fMRI studies showing dysfunction in dorsal-caudal putamen-mediated sensorimotor processing and inhibition (van Velzen et al., 2014) and posterior insula–mediated interoception and integration of sensory information in OCD (Nagai et al., 2007). Thus, the findings extend current theories of fronto-striatal dysregulation in OCD, suggesting poor frontal lobe-mediated control over overactive striato-limbic activation in ventral and dorsal subregions of the BG, affecting motivation and affect as well as sensorimotor processing, respectively, ultimately resulting in poor control over obsessions, compulsions and anxiety by showing that this is disorder-specific to OCD. In ASD patients, by contrast, the shared reduced r/dACC/MPFC was concomitant with reduced structure in the right hemisphere homologue BG/insula regions relative to controls and OCD, suggesting a structural reduction in ASD of the entire r/d/MPFC/ACC-striato-limbic network as opposed to fronto-striatal dysregulation in OCD. Anterior insula and BG form

part of inferior fronto-striatal inhibitory networks in children and adults (Rubia et al., 2013, Cai et al., 2014, Dambacher et al., 2014, Hugdahl et al., 2015) and are important for salience detection, motivation and habit-learning (Cai et al., 2014, Gillan and Robbins, 2014). In OCD, multimodal overlap of enhanced BG structure and function extends findings that enlarged BG volumes are related to poor inhibitory control (Menzies et al., 2007) and that increased bottom-up influence of posterior insula and BG drives enhanced habit-based responses and altered interoceptive processing at the expense of externally-motivated goal-directed actions such as inhibitory control (Fineberg et al., 2014). There is also evidence in OCD of enhanced striatal synaptic dopamine, which may be related to hyperactivation and enhanced volumes (Nikolaus et al., 2010). In ASD, anterior insula underactivation has been linked to abnormalities in saliency processing (Di Martino et al., 2009). Thus, disorder-specific findings of enhanced insula/BG function and structure in OCD relative to ASD patients and controls, but reduced right insula/BG volume in ASD relative to controls are in line with predominant theories of fronto-striatal dysregulation in OCD involving reduced ventromedial prefrontal control over enhanced striato-insular structure and function linked to interoceptive abnormalities (Fineberg et al., 2014) and with evidence for overall reduced function and structure in these regions in ASD (Uddin and Menon, 2009), suggesting abnormalities in the saliency network. Importantly, the findings suggest that a shared neurocognitive phenotype of poor top-down inhibitory control over behaviour and affect is underpinned by differing underlying structural and functional fronto-striato-insular networks in the two disorders.

Disorder-differentiated structural abnormalities were also observed in left superior frontal gyrus, which was decreased in GMV in OCD versus ASD patients and controls but increased in GMV in ASD versus controls. This extends a previous VBM meta-analysis (Rotge et al., 2010) by showing that superior frontal GMV reduction is disorder-specific relative to ASD patients, who typically have enhanced dorsal and superior frontal volumes (Courchesne et al., 2007), which furthermore correlated with ASD symptom severity (Rojas et al., 2006). Enhanced frontal volumes in ASD also extends evidence of early frontal grey matter overgrowth which appears arrested later in life (Courchesne et al., 2007).

In fMRI, left DLPFC activation was disorder-specifically reduced in ASD patients relative to controls and OCD patients. Left DLPFC is involved in goal representation and attention selection as well as response inhibition and maintenance of stimulus representations in the presence of distracting or interfering events (Ridderinkhof et al., 2004). DLPFC hypoactivation has been observed in ASD during cognitive control tasks involving inhibition (Kana et al., 2007), attention (Silk et al., 2006, Christakou et al., 2013b) and working-memory (Di Martino et al., 2009, Stigler et al., 2011). We previously found that left DLPFC hypoactivation in ASD is associated and anti-correlated with increased PCC activation during sustained attention (Christakou et al., 2013b), which was also enhanced in this meta-analysis in ASD relative to controls and OCD. PCC is a key node in the default mode network (DMN) thought to reflect task-irrelevant thinking and typically less deactivated during cognitive tasks in ASD (Minshew and Keller, 2010), including attention (Gadgil et al., 2013) and interference inhibition (Kennedy et al., 2006), presumably reflecting increased mind wandering. Here, we show that decreased left

DLPFC activation together with reduced deactivation of DMN regions including PCC is disorder-specific to ASD and may be related to attention problems typically observed in the disorder (Christakou et al., 2013b), although DMN abnormalities have also been observed in OCD (Menzies et al., 2008, Stern and Taylor, 2014).

OCD patients showed disorder-specific decreased inhibitory activation relative to ASD patients and controls in right STL and left IPL, extending findings of temporo-parietal underactivation during interference inhibition (Nakao et al., 2005, Woolley et al., 2008, Page et al., 2009), response inhibition (Roth et al., 2007), planning (van den Heuvel et al., 2005b), and switching (Menzies et al., 2008). Superior temporal and IPL regions presumably are involved during inhibition tasks due to their function in visual-spatial attention to salient stimuli (Rubia et al., 2006, Rubia et al., 2011). It has been argued that while there is enhanced salience processing of disorder-relevant and symptom-triggering stimuli in OCD (e.g. contamination for compulsive washers), there is reduced visual-spatial saliency processing in posterior visual-spatial attention regions during cognitive tasks, presumably due to the over-recruitment of these regions in relation to symptom-related saliency (Menzies et al., 2008, Rubia et al., 2011), which likely underlies poor performance on selective attention and inhibitory control tasks (Chamberlain et al., 2005). The findings suggest disorder-dissociated reduced recruitment of DLPFC in ASD and temporo-parietal regions in OCD during inhibitory control, presumably underlying their respective attention problems.

This study has several limitations. This study was based primarily on peak coordinates, as statistical brain maps were difficult to obtain. Studies used different statistical thresholds, so that weak group differences may be lost from studies using conservative thresholds which may have led to decreased statistical power. This is however counterbalanced by the large number of included studies. We also acknowledge that, as whole-brain analyses may be underpowered to detect differences within specific ROIs, our meta-analysis cannot discount the absence of other findings reported in ROI-based studies, such as ACC hyperactivation/failure of deactivation that has previously been observed in OCD patients compared to controls during tasks of cognitive control (e.g. (Ursu et al., 2003, Maltby et al., 2005, Fitzgerald et al., 2010). ASD studies included younger and more male patients. However, this was controlled for by covariance analyses and sex and age-matched subgroup meta-analyses. Areas that did not survive these subgroup analyses were not discussed. Additionally, although inclusion criteria tried to rule out the possibility of comorbidity between OCD and ASD, it is possible that some OCD studies did not screen for ASD comorbidity or that ASD studies conflated OCD symptoms with the broader ASD phenotype. This might have reduced the disorder-specific findings. The combination of different fMRI tasks within the same inhibitory control domain presents some variability. However, findings survived when task-type was covaried. Moreover, common fronto-striato-parietal activation patterns underlie these different inhibitory control tasks (Hugdahl et al., 2015). Furthermore, given evidence for developmental differences in brain structure in both OCD (deWit et al., 2014) and ASD (Courchesne et al., 2011), it would have been interesting to conduct sub-meta-analyses of paediatric and adult subsamples. For example,

a recent mega-analysis in OCD found that GMV in putamen, insula and OFC declined with increasing age in controls but not OCD patients (deWit et al., 2014). However, due to the small number of paediatric studies, particularly in the fMRI sample (e.g. 4 OCD studies), results would have been underpowered. Nonetheless, developmental factors should be considered in future meta-analyses once more paediatric studies are available.

4.5 Conclusions

This comparative multimodal meta-analysis shows that different fronto-striato-insular abnormalities underlie seemingly similar behavioural phenotypes in ASD and OCD. They share functional and structural abnormalities in r/dACC/MPFC. However, they differ in functional and structural abnormalities in BG/insula which were increased in OCD, in line with medial fronto-striatal dysregulation models of poor top-down frontal control over hyperactive striato-limbic regions while in ASD, they were decreased, suggesting reduced function and structure in medial fronto-striato-limbic networks.

4.6 Supplementary information

As this chapter has been previously published, supplementary information is presented as available online, separate from the main text of Chapter 4:

DOI: http://dx.doi.org/10.1016/j.biopsych.2016.10.006

4.6.1 Supplementary methods

4.6.1.1 Estimation of the mean of the effect-sizes of the different functional tasks, and its variance accounting for the number of tasks and the correlation among them

Note: the following formulas would be separately applied to each voxel of the brain map.

Some datasets included multiple inhibition contrasts (Morein-Zamir et al., 2015), and some studies included used different functional tasks in the same (or mostly overlapping) sets of patients and controls (Schmitz et al., 2006, Woolley et al., 2008, Page et al., 2009), or compared patient subgroups against the same set of controls (Subirà et al., 2013, Hashimoto et al., 2014).

In previous meta-analyses (Rubia et al., 2014) we calculated the effect size of the "mean brain response to the different functional tasks." However, it may be shown that the variance associated to this mean brain response is lower than the variance associated to one task (see demonstration below). This increase in precision implies an increase of the effect size, which could be a source of meta-analytic heterogeneity. To overcome this artificial, methodological heterogeneity, this study adopted a new approach consisting of simply

calculating the arithmetic mean of the effect size of the different functional tasks but then adjusting its variance accounting for the number of tasks and the correlation among them so that the combined study has the same statistical significance (*z*-value) as when using the effect size of the mean response. In other words, the effect size reflects the response of an individual to a task, and the fact that the combined study includes several tasks reduces the variance in a similar way that large samples do. This new simple approach will be included in the next version of the SDM software to allow other researchers to conduct repeated-measures meta-analyses. Please find steps below.

Sample mean and variance of the mean brain response to different functional tasks in one group

The mean brain response of the i^{th} participant to the different functional tasks is:

$$m_i = \frac{1}{N}\sum_{j=1}^{N} x_{ij}$$

where N is the number of functional tasks, and x_{ij} is the brain response of the i^{th} participant to the j^{th} functional task.

The sample mean of the mean brain response to the different functional tasks is:

$$\bar{m} = \frac{1}{n}\sum_{i=1}^{n} m_i = \frac{1}{n}\sum_{i=1}^{n}\left(\frac{1}{N}\sum_{j=1}^{N} x_{ij}\right) = \frac{1}{N}\sum_{j=1}^{N}\left(\frac{1}{n}\sum_{i=1}^{n} x_{ij}\right) = \frac{1}{N}\sum_{j=1}^{N}\bar{x}_j$$

where n is the number of participants, and $\bar{x}_j$ is the sample mean of the brain response to the j^{th} functional task.

The sample variance of the mean brain response to the different functional tasks is:

$$
\begin{aligned}
s_m^2 &= \frac{n}{n-1}\left(\frac{1}{n}\sum_{i=1}^{n} m_i^2 - \bar{m}^2\right) \\
&= \frac{n}{n-1}\left(\frac{1}{n}\sum_{i=1}^{n}\left(\frac{1}{N}\sum_{j=1}^{N} x_{ij}\right)^2 - \left(\frac{1}{N}\sum_{j=1}^{N}\bar{x}_j\right)^2\right) \\
&= \frac{1}{N^2}\frac{n}{n-1}\left(\frac{1}{n}\sum_{i=1}^{n}\left(\sum_{j=1}^{N} x_{ij}^2 + 2\sum_{j_1=1}^{N-1}\sum_{j_2=j_1+1}^{N} x_{ij_1}x_{ij_2}\right) - \left(\sum_{j=1}^{N}\bar{x}_j^2 + 2\sum_{j_1=1}^{N-1}\sum_{j_2=j_1+1}^{N}\bar{x}_{j_1}\bar{x}_{j_2}\right)\right) \\
&= \frac{1}{N^2}\frac{n}{n-1}\left(\frac{1}{n}\sum_{i=1}^{n}\sum_{j=1}^{N} x_{ij}^2 + 2\frac{1}{n}\sum_{i=1}^{n}\sum_{j_1=1}^{N-1}\sum_{j_2=j_1+1}^{N} x_{ij_1}x_{ij_2} - \sum_{j=1}^{N}\bar{x}_j^2 - 2\sum_{j_1=1}^{N-1}\sum_{j_2=j_1+1}^{N}\bar{x}_{j_1}\bar{x}_{j_2}\right) \\
&= \frac{1}{N^2}\frac{n}{n-1}\left(\sum_{j=1}^{N}\left(\frac{1}{n}\sum_{i=1}^{n} x_{ij}^2 - \bar{x}_j^2\right) + 2\sum_{j_1=1}^{N-1}\sum_{j_2=j_1+1}^{N}\left(\frac{1}{n}\sum_{i=1}^{n} x_{ij_1}x_{ij_2} - \bar{x}_{j_1}\bar{x}_{j_2}\right)\right) \\
&= \frac{1}{N^2}\left(\sum_{j=1}^{N}\frac{n}{n-1}\left(\frac{1}{n}\sum_{i=1}^{n} x_{ij}^2 - \bar{x}_j^2\right) + 2\sum_{j_1=1}^{N-1}\sum_{j_2=j_1+1}^{N}\frac{n}{n-1}\left(\frac{1}{n}\sum_{i=1}^{n} x_{ij_1}x_{ij_2} - \bar{x}_{j_1}\bar{x}_{j_2}\right)\right) \\
&= \frac{1}{N^2}\left(\sum_{j=1}^{N} s_j^2 + 2\sum_{j_1=1}^{N-1}\sum_{j_2=j_1+1}^{N} s_{j_1,j_2}\right) \\
&= \frac{1}{N^2}\left(\sum_{j=1}^{N} s_j^2 + 2\sum_{j_1=1}^{N-1}\sum_{j_2=j_1+1}^{N} s_{j_1}s_{j_2}r_{j_1,j_2}\right)
\end{aligned}
$$

where s_j^2 is the sample variance of the brain response to the j^{th} functional task, s_{j_1,j_2} is the sample covariance between the brain responses to the $j_1{}^{th}$ and $j_2{}^{nd}$ functional tasks, and r_{j_1,j_2} is the sample correlation between the brain responses to the $j_1{}^{th}$ and $j_2{}^{nd}$ functional tasks.

The specific s_j and r_{j_1,j_2} are usually unknown, but the expression may be greatly simplified under the general assumption that sample variances and correlations are similar across the different functional tasks and groups:

$$\begin{aligned} s_m^2 &= \frac{1}{N^2}\left(\sum_{j=1}^{N} s_j^2 + 2\sum_{j_1=1}^{N-1}\sum_{j_2=j_1+1}^{N} s_{j_1} s_{j_2} r_{j_1,j_2}\right) \\ &\approx \frac{1}{N^2}\left(\sum_{j=1}^{N} s^2 + 2\sum_{j_1=1}^{N-1}\sum_{j_2=j_1+1}^{N} s^2 r\right) \\ &= \frac{1}{N^2}\left(N \cdot s^2 + 2 \cdot \frac{N(N-1)}{2} \cdot s^2 r\right) \\ &= \frac{1+(N-1)\cdot r}{N} \cdot s^2 \\ &= VR_{N,r} \cdot s^2 \end{aligned}$$

where $VR_{N,r}$ is the variance reduction associated to the specific N and r. Note that if $r < 1$ (i.e. the brain response is not identical between tasks), then $VR_{N,r} < 1$, i.e. the variance associated to the mean brain response is lower than the variance associated to the response to one task.

Sample effect size of the difference in brain response to different functional tasks

The sample effect size of the difference in the mean brain response to the different functional tasks is:

$$
\begin{aligned}
d_m^* &= \frac{\overline{m_p} - \overline{m_c}}{s_m} = \frac{\frac{1}{N}\sum_{j=1}^{N}\bar{x}_{j,p} - \frac{1}{N}\sum_{j=1}^{N_0}\bar{x}_{j,c}}{\sqrt{\frac{(n_p-1)\cdot s_{m,p}^2 + (n_c-1)\cdot s_{m,c}^2}{n_p+n_c-2}}} \\
&= \frac{\frac{1}{N}\sum_{j=1}^{N}\left(\bar{x}_{j,p} - \bar{x}_{j,c}\right)}{\sqrt{\frac{(n_p-1)\cdot VR_{N,r}\cdot s_p^2 + (n_c-1)\cdot VR_{N,r}\cdot s_c^2}{n_p+n_c-2}}} \\
&= \frac{\frac{1}{N}\sum_{j=1}^{N} d_j^* \cdot s_j}{\sqrt{VR_{N,r}\cdot\frac{(n_p-1)\cdot s_p^2 + (n_c-1)\cdot s_c^2}{n_p+n_c-2}}} \\
&\approx \frac{\frac{1}{N}\sum_{j=1}^{N} d_j^* \cdot s}{\sqrt{VR_{N,r}\cdot s^2}} \\
&= \frac{1}{\sqrt{VR_{N,r}}}\cdot\frac{1}{N}\sum_{j=1}^{N} d_j^* \\
&= \frac{1}{\sqrt{VR_{N,r}}}\cdot\overline{d^*}
\end{aligned}
$$

where d_j^* is the sample effect size of the difference in brain response to the j^{th} functional task, sub-indexes "p" and "c" refer to patients and controls, and sample variances have been assumed to be similar.

The *z*-value for this effect size is:

$$
\begin{aligned}
z(d_m) &= \frac{d_m}{\sqrt{\sigma^2\left(d_m\right)}} \\
&= \frac{J_{df} \cdot d_m^*}{\sqrt{\sigma^2\left(J_{df} \cdot d_m^*\right)}} \\
&= \frac{J_{df} \cdot d_m^*}{\sqrt{\left(\frac{1}{n_1}+\frac{1}{n_2}\right)+\left(1-\frac{df-2}{df \cdot J_{df}^2}\right) \cdot \left(J_{df} \cdot d_m^*\right)^2}} \\
&= \frac{J_{df} \cdot \frac{1}{\sqrt{VR_{N,r}}} \cdot \overline{d^*}}{\sqrt{\left(\frac{1}{n_1}+\frac{1}{n_2}\right)+\left(1-\frac{df-2}{df \cdot J_{df}^2}\right) \cdot \left(J_{df} \cdot \frac{1}{\sqrt{VR_{N,r}}} \cdot \overline{d^*}\right)^2}} \\
&= \frac{J_{df} \cdot \overline{d^*}}{\sqrt{VR_{N,r} \cdot \left(\frac{1}{n_1}+\frac{1}{n_2}\right)+\left(1-\frac{df-2}{df \cdot J_{df}^2}\right) \cdot \left(J_{df} \cdot \overline{d^*}\right)^2}} \\
&= \frac{\overline{d}}{\sqrt{VR_{N,r} \cdot \left(\frac{1}{n_1}+\frac{1}{n_2}\right)+\left(1-\frac{df-2}{df \cdot J_{df}^2}\right) \cdot \overline{d}^2}} \\
&= \frac{\overline{d}}{\sqrt{\sigma^2_{modified}\left(\overline{d}\right)}}
\end{aligned}
$$

where d_m is the effect size of the difference in the mean brain response to the different functional tasks, J_{df} is the bias correction, $\sigma^2(d)$ is the estimated variance of d, and $\overline{d}$ is the simple arithmetic mean of the effect sizes. Thus if, in order to keep the effect size in the range of the effect size of the remaining studies, we calculate the simple arithmetic mean of the effect sizes, the same *z*-value may be obtained using the modified variance:

$$\sigma^2_{modified}(d) = VR_{N,r} \cdot \left(\frac{1}{n_1} + \frac{1}{n_2}\right) + \left(1 - \frac{df - 2}{df \cdot J^2_{df}}\right) \cdot d^2$$

4.6.1.2 Assumption of similar sample variances and correlations

The method rests partly upon the general assumption that sample variances and correlations are similar across the different functional tasks and groups. To our knowledge, there is no reason to rely on other, more complex assumptions (e.g. to consider sample variance in patients to be twice the variance in controls), and the method seems robust to violations of the assumption. For instance, when combining the effect sizes of 20 patients relative to 20 controls performing two tasks with similar effect size, the variance reduction factor under the general assumption is 0.65. Differences in sample variances or correlations between groups have a negligible or null effect, e.g. the variance reduction factor is ~0.65 if the correlation in patients is twice the correlation in controls, and again ~0.65 if the variance in patients is twice the variance in controls. Differences in variances between tasks have a larger effect, but this is still mild even when differences are large, e.g. the variance reduction factor is ~0.69 if the variance in one task is twice the variance in the other task.

4.6.1.3 Study selection: search terms

PubMed, ScienceDirect, Scopus and Google Scholar databases were searched by authors CC, LN and SL using either keywords related to OCD (“obsessive-compulsive disorder”, “OCD”, “obsessive”, “compulsive”) or ASD (“autism”, “autistic”, “Asperger”, “ASD”, “autism spectrum disorder”, “pervasive developmental disorder”) plus terms

associated with structural imaging ("VBM", "voxel-based morphometry", "voxel-wise", "structural MRI", "grey matter") to generate a list of structural MRI studies. The same diagnostic keywords were used in combination with terms related to cognitive and motor inhibition ("executive function", "inhibition", "stroop task", "cognitive control", "stop task", "go/no-go task", "flanker", "task-switching", "inhibitory control") plus terms for functional imaging ("fMRI", "functional", "brain function") to obtain a list of fMRI studies investigating inhibition. Citations within obtained articles revealed additional studies. Obtained articles were cross-referenced and agreed upon by CC, LN and SL to confirm inclusion criteria were met.

Studies which used ROI analysis were not included, as examining previously defined regions of interest limits the search towards *a priori* hypothesized regions, thereby providing a biased and inappropriately constrained characterization of anatomy or function (Friston et al., 2006).

4.6.1.4 Statistical methods

From each study, the peak coordinates (i.e. maximum difference in GMV or activation between patients and controls) of significant clusters at whole-brain level were included. The strict criteria employed by SDM of selecting only those coordinates significant at the whole-brain level aim to avoid bias towards liberally thresholded regions, as is often seen in ROI analysis. In studies where both corrected and uncorrected statistics were reported, the more liberal threshold from uncorrected results was used. Montreal Neurological Institute (MNI) coordinates were converted to Talairach space using matrix

transformations (Lancaster et al., 2007). Once coordinates were identified and converted to Talairach space, a map of differences in either GMV or blood oxygen level-dependent (BOLD) activation was recreated for each individual study. SDM uses a 25mm full-width at half maximum (FWHM) un-normalized Gaussian kernel assigning higher values to the voxels closer to peaks, as it has been found to have an excellent control of false positives (Salimi-Khorshidi et al., 2009).

The analysis of covariance (ANCOVA) of regional GMV and activation differences with age and gender resulted in a *Q*-statistic (similar to an *F*-statistic) for each region as well as a map summarizing these effects and a *z*-statistic for the difference between males and females or older and younger participants.

The aim of the conjunction/disjunction analysis was not to detect correlations between activation and GMV or in either of these between OCD and ASD, but rather to detect those regions showing abnormalities in both disorders or modalities (Radua et al., 2014a).

Subgroup analysis was performed by matching groups on age and sex. Specifically, a script iteratively evaluated all possible subsets of n-1 studies and selected the one in which the minimum *p*-value was largest. Selection of the subset was conditioned to maintain a balance between ASD and OCD studies and to avoid exclusion of studies with SPM maps given that they optimally increase the power of a meta-analysis.

4.6.2 Supplementary results

4.6.2.1 Results of literature search

For a complete list of included studies and study details, see Table 4.1 Demographic and clinical characteristics of included studies in the main text of Chapter 4. The search retrieved a total of thirty-two useable ASD VBM datasets and thirty useable OCD VBM datasets. Seven studies used only region of interest methods and were therefore excluded (Hardan et al., 2003, Salmond et al., 2005, Nishida et al., 2011, Brooks et al., 2015, D'Mello et al., 2015, Goddard et al., 2015, Libero et al., 2015). Eleven studies were excluded as they did not provide pairwise univariate voxel-wise comparisons of OCD or ASD patients with a control group (Salmond et al., 2005, Lázaro et al., 2009, Uddin et al., 2011, Alvarenga et al., 2012, Benedetti et al., 2012, Alonso et al., 2013, Hoexter et al., 2013, Liu et al., 2014, Parrado-Hernández et al., 2014, Banks et al., 2015, Cheng et al., 2015). One OCD study was excluded as it included fewer than 10 patients (Chen et al., 2013), and two ASD studies were excluded as the ASD samples were inappropriate for the purposes of this meta-analyses (one included patients with comorbid OCD (Riedel et al., 2014) and the other included intellectually disabled individuals with autistic traits rather than a diagnosis of ASD (Spencer et al., 2006)). Five studies contained overlapping patient samples and were excluded, including a mega-analysis containing data much of which had been published previously (Kim et al., 2001, Ecker et al., 2010, Riva et al., 2013, deWit et al., 2014, Huyser et al., 2014).

The ASD fMRI search retrieved a total of twelve useable datasets, while the OCD fMRI search retrieved a total of fourteen useable datasets. A further six studies which did not compare patient groups using whole-brain image analysis methods were excluded (Maltby et al., 2005, Thakkar et al., 2008, Solomon et al., 2009, Agam et al., 2010, de Wit et al., 2012, Remijnse et al., 2013), along with five studies which did not include a pairwise whole-brain comparison of ASD or OCD patients against healthy controls (Dichter and Belger, 2007, Rubia et al., 2010a, Rubia et al., 2011, Vriend et al., 2013, Tolin et al., 2014), three datasets which included duplicated patient data (Nabeyama et al., 2008, Nakao et al., 2009b, Han et al., 2011), two studies which used fewer than 10 patients (Belmonte and Yurgelun-Todd, 2003, Fitzgerald et al., 2005), and six studies that did not include a suitable inhibition contrast (Haist et al., 2005, van den Heuvel et al., 2005a, Goldberg et al., 2011, Grützmann et al., Berlin et al., 2015, Brennan et al., 2015).

4.6.2.2 Matched subgroup analyses

Meta-analyses were repeated on a subset of studies matched on age and sex per the methods outlined in the main text so that groups did not significantly differ on either variable (p>.05). Matching ASD and OCD VBM studies on age and sex resulted in the exclusion of 17 ASD studies (Boddaert et al., 2004, Kwon et al., 2004, Waiter et al., 2004, Rojas et al., 2006, Brieber et al., 2007, McAlonan et al., 2008, Langen et al., 2009, Hyde et al., 2010, Kosaka et al., 2010, Toal et al., 2010, Kurth et al., 2011, Mengotti et al., 2011, Ecker et al., 2012, Greimel et al., 2013, Foster et al., 2015, Gori et al., 2015, Itahashi et al., 2015) and 14 OCD studies (Pujol et al., 2004, Riffkin et al., 2005, Valente Jr et al., 2005, Christian et al., 2008, Gilbert et al., 2008b, Szeszko et al., 2008, van den Heuvel et al., 2009, Togao et al., 2010, Exner et al., 2012, Hoexter et al., 2013, Huyser et al., 2013, Subirà et al., 2013, Hashimoto et al., 2014, Okada et al., 2015). Matching OCD and ASD fMRI studies on age and sex resulted in the exclusion of 3 ASD studies and 6 OCD studies. Results of these analyses are presented in Figure 4.2 as well as Table 4.5 and Table 4.6.

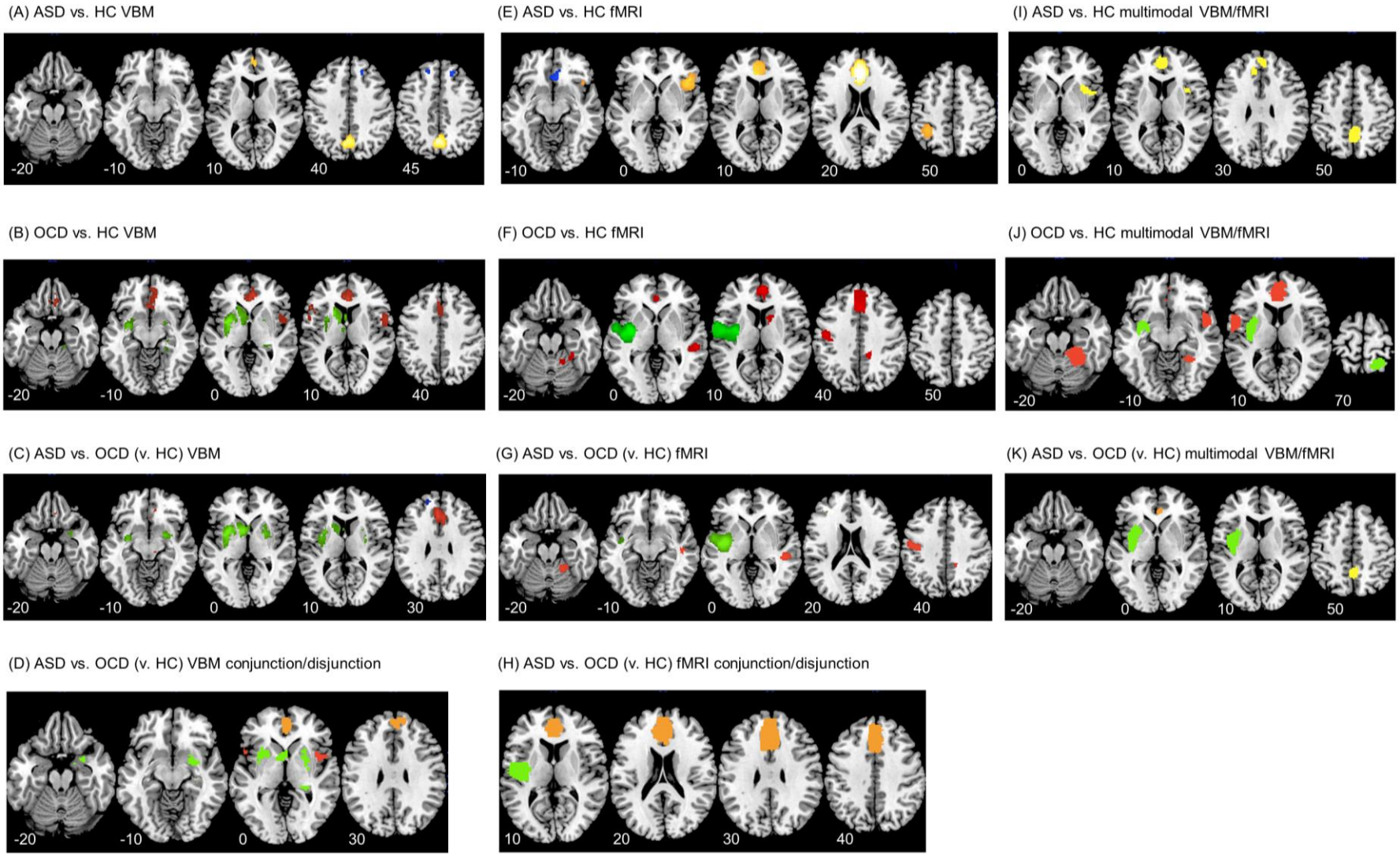

(A) ASD vs. HC VBM
-20 -10 10 40 45
(E) ASD vs. HC fMRI
-10 0 10 20 50
(I) ASD vs. HC multimodal VBM/fMRI
0 10 30 50
(B) OCD vs. HC VBM
-20 -10 0 10 40
(F) OCD vs. HC fMRI
-20 0 10 40 50
(J) OCD vs. HC multimodal VBM/fMRI
-20 -10 10 70
(C) ASD vs. OCD (v. HC) VBM
-20 -10 0 10 30
(G) ASD vs. OCD (v. HC) fMRI
-20 -10 0 20 40
(K) ASD vs. OCD (v. HC) multimodal VBM/fMRI
-20 0 10 50
(D) ASD vs. OCD (v. HC) VBM conjunction/disjunction
-20 -10 0 30
(H) ASD vs. OCD (v. HC) fMRI conjunction/disjunction
10 20 30 40

Figure 4.2 Whole-brain age- and sex-matched subgroup meta-analysis of VBM and fMRI differences between ASD, OCD and controls

(A) VBM meta-analysis results for a subgroup of ASD patients relative to controls. (B) VBM meta-analysis results for a subgroup of OCD patients relative to controls. (C) VBM meta-analysis results for the age- and sex-matched subgroup comparison between ASD patients (vs. controls) and OCD patients (vs. controls). (D) Age- and sex-matched subgroup VBM meta-analysis results for conjunction/disjunction analysis of ASD and OCD abnormalities (vs. controls). (E) fMRI meta-analysis results for a subgroup of ASD patients relative to controls. (F) fMRI meta-analysis results for a subgroup of OCD patients relative to controls. (G) Subgroup fMRI meta-analysis results for the age- and sex-matched comparison between ASD (vs. controls) and OCD (vs. controls). (H) Age- and sex-matched subgroup fMRI meta-analysis results for conjunction/disjunction analysis of ASD and OCD abnormalities (vs. controls). (I) Age and sex-matched subgroup fMRI-VBM multimodal conjunction/disjunction analysis showing overlapping abnormalities in ASD relative to controls. (J) Age- and sex-matched subgroup fMRI-VBM multimodal conjunction/disjunction analysis showing overlapping abnormalities in OCD relative to controls. (K) Age- and sex-matched subgroup fMRI-VBM multimodal conjunction/disjunction analysis for the comparison between ASD (vs. controls) and OCD (vs. controls). Cool colors (blue in ASD, green in OCD) indicate increased brain structure or function in patients versus controls. Warm colors (yellow in ASD, red in OCD) indicate decreased brain structure or function in patients versus controls. For (D) and (H), orange indicates disorder-shared decreases in structure/function, respectively.

Table 4.5 Meta-analysis results for a subgroup of age and sex-matched VBM studies in ASD and OCD

Contrast	Brodmann areas	MNI x,y,z coordinates	SDM *z*-score	*P* value	No. of voxels
(A) ASD versus HC					
ASD < HC					
Precuneus	7	-2,-64,48	-1.742	<.001	650
r/d ACC/MPFC	32/9/10	-2,52,16	-1.578	<.001	309
L MFG	8/9	-46,16,28	-1.390	.002	28
R putamen/BG	-	28,10,4	-1.331	.003	14
ASD > HC					
L MFG	9	-18,48,28	1.613	<.001	102
R MFG	9	18,34,42	1.605	<.001	45
L MFG/DLPFC	8	-16,38,44	1.389	.002	23
R precentral gyrus	6	20,-2,60	1.393	.002	23
R cerebellum	-	6,-76,-28	1.292	.004	11
(B) OCD versus HC					
OCD < HC					
v/r/d ACC/MPFC	25/11/24/32/9	0,22,22	-2.791	<.0001	2259
R insula/premotor cortex/STL	6/44/22	58,6,12	-2.001	<.001	479
L insula/premotor cortex/VLPFC	6/44/45	-52,20,14	-1.822	.001	114
R anterior insula	47	34,24,-4	-1.769	.002	18
OCD > HC					
L insula/BG/amygdala	-	-28,4,-2	2.381	<.0001	1577
R superior parietal gyrus	7	16,-56,72	1.668	<.001	122
R thalamus	-	24,-30,-2	1.695	<.001	136
L superior parietal gyrus	5/7	-18,-46,70	1.436	<.001	98
R insula/BG/amygdala	-	22,0,-6	1.642	<.001	79

(C) ASD (vs. HC) versus OCD (vs. HC)					
ASD (vs. HC) < OCD (vs. HC)					
L insula/BG/amygdala	-	-28,4,-2	-2.036	<.0001	883
Precuneus	7	0,-66,42	-1.778	<.0001	603
L caudate	-	-6,10,2	-1.976	<.0001	462
R insula/BG/amygdala	-	24,4,-2	-1.772	<.0001	479
R postcentral gyrus/IPL	3/1/2/7	44,-28,44	-1.224	.002	51
ASD (vs. HC) > OCD (vs. HC)					
r/d ACC/MPFC	24/32	6,28,24	2.267	<.0001	678
vmOFC	11/32	10,36,-8	1.746	<.001	28
L MFG/DLPFC	9	-16,48,30	1.629	.001	26
R MFG	8/9	20,36,44	1.565	.002	22
vmOFC	11	8,32,-18	1.596	.002	17

Abbreviations: ACC, anterior cingulate cortex; ASD, autism spectrum disorders; BG, basal ganglia; d, dorsal; HC, healthy controls; IPL, inferior parietal lobe; L, left; MPFC, medial prefrontal cortex; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; No., number; OCD, obsessive compulsive disorder; R, right; r, rostral; STL, superior temporal lobe; v, ventral; VLPFC, ventrolateral prefrontal cortex; vmOFC, ventromedial orbitofrontal cortex; VBM, voxel-based morphometry

Table 4.6 Meta-analysis results for a subgroup of age and sex-matched fMRI studies in ASD and OCD

Contrast	Brodmann areas	MNI x,y,z coordinates	SDM *z*-score	*P* value	No. of voxels
(A) ASD versus HC					
ASD < HC					
r/d ACC/MPFC	32/24/9	0,32,22	-1.977	<.0001	2596
R VLPFC/anterior insula	47	46,24,0	-1.620	<.001	476
L IPL	40/7	-34,-46,52	-1.475	.001	366
L DLPFC/MFG	46/9	-40,34,32	-1.452	.001	239
ASD > HC					
vmOFC	11	-4,40,-16	1.006	<.001	488
(B) OCD versus HC					
OCD < HC					
v/r/d ACC/MPFC	10/9/32/24	-10,24,28	-2.601	<.0001	1804
L postcentral gyrus	3/1/2	-44,-14,36	-2.366	<.001	258
R STL/middle temporal gyrus	21/22	46,-20,-12	-2.439	<.001	261
R STL	21/22	54,6,-10	-2.076	.002	86
R fusiform gyrus	37	30,-46,-14	-2.053	.002	71
R PCC	23/31	14,-42,40	-2.235	<.001	65
R caudate/BG	-	12,2,12	-2.037	.002	58
R cerebellum IV/V	-	16,-50,-20	-1.924	.004	14
OCD > HC					
L insula/putamen/premotor cortex/precentral/VLPFC/STL	6/44/22	-58,-4,4	1.833	<.0001	1909
R superior parietal gyrus	7	18,-54,70	1.244	.001	40
L superior parietal gyrus	7	-20,-60,70	1.256	<.001	29
L cerebellum	-	-26,-50,-34	1.051	.003	14

(C) ASD (vs. HC) versus OCD (vs. HC)					
ASD (vs. HC) < OCD (vs. HC)					
L insula/putamen/premotor cortex/precentral/VLPFC/STL	6/44/22	-34,-8,4	-2.026	<.0001	2067
L MFG	9/46	-38,36,26	-1.445	<.001	212
ASD (vs. HC) > OCD (vs. HC)					
L pre/postcentral gyrus	6/4/3/1/2	-46,-14,38	1.850	<.001	253
R middle temporal lobe	21	46,-28,-2	1.834	<.001	216
R cerebellum IV/V	-	20,-46,-20	1.682	.002	99
vmOFC	11/25	2,28,-4	1.661	.002	69
R PCC	23/31	16,-42,36	1.735	.001	21

Abbreviations: ACC, anterior cingulate cortex; ASD, autism spectrum disorders; BG, basal ganglia; d, dorsal; HC, healthy controls; IPL, inferior parietal lobe; L, left; MPFC, medial prefrontal cortex; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; No., number; OCD, obsessive compulsive disorder; R, right; r, rostral; STL, superior temporal lobe; v, ventral; VLPFC, ventrolateral prefrontal cortex; vmOFC, ventromedial orbitofrontal cortex; VBM, voxel-based morphometry

4.6.2.3 Reliability analysis

A whole-brain jackknife sensitivity analysis for ASD VBM studies showed that the finding of increased GMV in left middle and superior temporal lobe was highly replicable and was preserved in all combinations of the datasets. The results of increased GMV in left MFG, left precentral gyrus and decreased GMV in r/dACC/MPFC were replicable in all but one combination, while the findings of increased GMV in right inferior temporal gyrus were replicated in all but two combinations. The right IPL/occipital cluster was replicated in all but three iterations, while the right precentral gyrus, right insula and left cerebellum were not as robustly replicated in jackknife analyses, with these clusters not replicated in 4 or more combinations (Table 4.7 and Table 4.8).

The jackknife analysis for the OCD VBM studies revealed that the findings of decreased GMV in v/r/d MPFC/ACC and left VLPFC/premotor cortex/insula/STL as well as increased GMV in the bilateral basal ganglia/insula were replicated in all combinations of studies. Decreased left MFG GMV and increased left cerebellum and right superior parietal lobe GMV survived all but one iteration. Decreased right IPL and increased right cerebellum GMV were present in all but two iterations. Left VLPFC was replicated in all but three combinations, while left postcentral gyrus and right cerebellum were less robust, with these clusters not replicated in 4 or more iterations of the analysis (Table 4.9 and Table 4.10).

FMRI whole-brain jackknife analyses revealed that clusters of reduced activation in ASD versus controls remained in all combinations for r/d ACC/MPFC and left DLPFC. Reduced right VLPFC/anterior insula activation and increased right inferior temporal/occipital lobe and left middle temporal gyrus activation were present in all but one combination of studies. Decreased left cerebellum, left IPL and left

MFG/premotor activation and increased precuneus/PCC activation was seen in all but two combinations of studies (Table 4.11 and Table 4.12).

In the OCD fMRI jackknife analysis, reduced activation in the v/r/d ACC/MPFC and right caudate survived all possible combinations. Decreased activation in right STL as well as increased activation in left insula/putamen/premotor/precentral/VLPFC/STL was preserved in all but one combination. Decreased right cerebellum and increased right precentral/premotor and left superior parietal activation were preserved in all but two combinations. Left postcentral gyrus and right PCC clusters were observed in all but three combinations (Table 4.13 and Table 4.14).

Table 4.7 Results of the reliability (jackknife) analyses for areas showing decreased GMV in ASD patients relative to healthy controls

	r/d ACC/MPFC/	R posterior insula	L cerebellum VIII
	4,44,16	44,-12,12	-10,-66,-48
Study			
(Abell et al., 1999)	yes	yes	yes
(McAlonan et al., 2002)	yes	no	yes
(Boddaert et al., 2004)	yes	yes	yes
(Waiter et al., 2004)	yes	yes	yes
(Kwon et al., 2004)	yes	yes	yes
(Rojas et al., 2006)	yes	yes	yes
(Schmitz et al., 2006)	yes	yes	yes
(Brieber et al., 2007)	yes	yes	no
(Craig et al., 2007)	yes	yes	yes
(Bonilha et al., 2008)	yes	yes	yes
(Freitag et al., 2008)	yes	yes	yes
(Ke et al., 2008)	yes	yes	yes
(McAlonan et al., 2008)	yes	yes	no
(Langen et al., 2009)	yes	yes	yes
(Wilson et al., 2009)	yes	yes	yes
(Toal et al., 2010)	yes	yes	no
(Hyde et al., 2010)	yes	yes	yes
(Kosaka et al., 2010)	yes	no	yes
(Mengotti et al., 2011)	yes	yes	yes
(Riva et al., 2011)	yes	no	yes
(Groen et al., 2011)	yes	yes	yes
(Kurth et al., 2011)	yes	yes	yes
(Poustka et al., 2012)	yes	yes	yes
(Calderoni et al., 2012)	yes	yes	yes

(Ecker et al., 2012)	yes	yes	yes
(Greimel et al., 2013)	no	yes	yes
(Mueller et al., 2013)	yes	yes	yes
(Poulin-Lord et al., 2014)	yes	yes	yes
(Lim et al., 2015)	yes	yes	no
(Gori et al., 2015)	yes	yes	yes
(Foster et al., 2015)	yes	no	no

Abbreviations: ASD, autism spectrum disorders; GMV, grey matter volume; L, left; R, right; r/dACC/MPFC, rostral/dorsal anterior cingulate cortex/medial prefrontal cortex

Table 4.8 Results of the reliability (jackknife) analyses for areas showing increased GMV in ASD patients relative to healthy controls

	L mid./ superior temporal lobe	R IPL/ occipital lobe	L mid. frontal gyrus	L precentral gyrus	R inf. temporal gyrus	R precentral gyrus
	-44,6,-26	50,-58,36	-20,30,46	-38,-14,50	60,-4,-14	34,-16,46
Study						
(Abell et al., 1999)	yes	yes	yes	yes	yes	yes
(McAlonan et al., 2002)	yes	no	yes	yes	yes	no
(Boddaert et al., 2004)	yes	yes	yes	yes	yes	yes
(Waiter et al., 2004)	yes	yes	yes	yes	yes	yes
(Kwon et al., 2004)	yes	yes	yes	yes	yes	yes
(Rojas et al., 2006)	yes	yes	yes	yes	yes	yes
(Schmitz et al., 2006)	yes	yes	yes	yes	yes	yes
(Brieber et al., 2007)	yes	yes	yes	yes	yes	yes
(Craig et al., 2007)	yes	yes	yes	yes	yes	no
(Bonilha et al., 2008)	yes	yes	yes	yes	yes	yes
(Freitag et al., 2008)	yes	yes	yes	yes	yes	yes
(Ke et al., 2008)	yes	no	yes	yes	yes	yes
(McAlonan et al., 2008)	yes	yes	yes	yes	yes	no
(Langen et al., 2009)	yes	yes	yes	yes	yes	yes
(Wilson et al., 2009)	yes	yes	yes	yes	yes	yes
(Toal et al., 2010)	yes	yes	yes	yes	yes	no
(Hyde et al., 2010)	yes	yes	yes	yes	yes	yes
(Kosaka et al., 2010)	yes	yes	yes	yes	yes	no
(Mengotti et al., 2011)	yes	no	yes	yes	yes	yes
(Riva et al., 2011)	yes	yes	yes	yes	yes	yes
(Groen et al., 2011)	yes	yes	yes	yes	yes	yes
(Kurth et al., 2011)	yes	yes	yes	yes	yes	yes
(Poustka et al., 2012)	yes	yes	yes	yes	yes	yes

(Calderoni et al., 2012)	yes	yes	yes	yes	yes	yes
(Ecker et al., 2012)	yes	yes	no	no	no	no
(Greimel et al., 2013)	yes	yes	yes	yes	yes	no
(Mueller et al., 2013)	yes	yes	yes	yes	yes	no
(Poulin-Lord et al., 2014)	yes	yes	yes	yes	yes	yes
(Lim et al., 2015)	yes	yes	yes	yes	no	no
(Gori et al., 2015)	yes	yes	yes	yes	yes	yes
(Foster et al., 2015)	yes	yes	yes	yes	yes	no

Abbreviations: ASD, autism spectrum disorders; GMV, grey matter volume; IPL, inferior parietal lobe; L, left; mid., middle; R, right

Table 4.9 Results of the reliability (jackknife) analyses for areas showing decreased GMV in OCD patients relative to healthy controls

Decreased GMV in OCD patients versus healthy controls					
	v/r/d ACC/MPFC	L VLPFC/ premotor/insula/STL	R IPL	L MFG/DLPFC	L VLPFC
	-2,30,34	-52,18,12	52,-56,38	-28,34,38	-44,44,-4
Study					
(Pujol et al., 2004)	yes	yes	yes	yes	yes
(Riffkin et al., 2005)	yes	yes	yes	yes	yes
(Valente Jr et al., 2005)	yes	yes	yes	yes	yes
(Carmona et al., 2007)	yes	yes	yes	yes	yes
(Soriano-Mas et al., 2007)	yes	yes	yes	yes	yes
(Yoo et al., 2008)	yes	yes	yes	yes	no
(Gilbert et al., 2008a)	yes	yes	yes	yes	yes
(Szeszko et al., 2008)	yes	yes	yes	yes	yes
(Christian et al., 2008)	yes	yes	yes	yes	yes
(Gilbert et al., 2008b)	yes	yes	yes	no	yes
(Kopřivová et al., 2009)	yes	yes	yes	yes	yes
(van den Heuvel et al., 2009)	yes	yes	yes	yes	no
(Matsumoto et al., 2010)	yes	yes	yes	yes	yes
(Britton et al., 2010)	yes	yes	yes	yes	yes
(Togao et al., 2010)	yes	yes	yes	yes	yes
(Lázaro et al., 2011)	yes	yes	yes	yes	yes
(Zarei et al., 2011)	yes	yes	yes	yes	yes
(Exner et al., 2012)	yes	yes	yes	yes	yes
(Hoexter et al., 2013)	yes	yes	no	yes	yes
(Huyser et al., 2013)	yes	yes	yes	yes	yes
(Hou et al., 2013)	yes	yes	yes	yes	yes
(Tan et al., 2013)	yes	yes	yes	yes	yes

(Subirà et al., 2013)	yes	yes	yes	yes	yes
(Tang et al., 2013)	yes	yes	yes	yes	yes
(Hashimoto et al., 2014)	yes	yes	yes	yes	yes
(Spalletta et al., 2014)	yes	yes	yes	yes	yes
(Okada et al., 2015)	yes	yes	no	yes	no
(Kim et al., 2015b)	yes	yes	yes	yes	yes
(Tang et al., 2015)	yes	yes	yes	yes	yes
(Jayarajan et al., 2015)	yes	yes	yes	yes	yes

Abbreviations: GMV, grey matter volume; IPL, inferior parietal lobe; L, left; MFG, middle frontal gyrus; OCD, obsessive compulsive disorder; R, right; STL, superior temporal lobe; v/r/d ACC/MPFC, ventral/rostral/dorsal anterior cingulate cortex/medial prefrontal cortex; VLPFC, ventrolateral prefrontal cortex

Table 4.10 Results of the reliability (jackknife) analyses for areas showing increased GMV in OCD patients relative to healthy controls

Increased GMV in OCD versus healthy controls							
	L insula/BG/ amygdala	R insula/BG/ amygdala	L cerebellum IV/V	R cerebellum IV/V	L postcentral	R superior parietal	R cerebellum
	-28,4,-2	24,4,-2	-14,-40,-20	12,-30,-22	-26,-36,62	16,-56,72	22,-38,-16
Study							
(Pujol et al., 2004)	yes	yes	no	yes	yes	yes	yes
(Riffkin et al., 2005)	yes	yes	yes	yes	yes	yes	yes
(Valente Jr et al., 2005)	yes	yes	yes	yes	yes	yes	no
(Carmona et al., 2007)	yes	yes	yes	yes	yes	yes	no
(Soriano-Mas et al., 2007)	yes	yes	yes	yes	yes	yes	yes
(Yoo et al., 2008)	yes	yes	yes	yes	no	no	yes
(Gilbert et al., 2008a)	yes	yes	yes	yes	yes	yes	yes
(Szeszko et al., 2008)	yes	yes	yes	yes	yes	yes	yes
(Christian et al., 2008)	yes	yes	yes	yes	yes	yes	yes
(Gilbert et al., 2008b)	yes	yes	yes	no	yes	yes	no
(Kopřivová et al., 2009)	yes	yes	yes	yes	no	yes	yes
(van den Heuvel et al., 2009)	yes	yes	yes	yes	yes	yes	no
(Matsumoto et al., 2010)	yes	yes	yes	yes	yes	yes	yes
(Britton et al., 2010)	yes	yes	yes	yes	yes	yes	yes
(Togao et al., 2010)	yes	yes	yes	yes	yes	yes	yes
(Lázaro et al., 2011)	yes	yes	yes	yes	yes	yes	yes
(Zarei et al., 2011)	yes	yes	yes	yes	yes	yes	yes
(Exner et al., 2012)	yes	yes	yes	yes	yes	yes	yes
(Hoexter et al., 2013)	yes	yes	yes	yes	no	yes	yes
(Huyser et al., 2013)	yes	yes	yes	yes	yes	yes	yes
(Hou et al., 2013)	yes	yes	yes	yes	yes	yes	yes
(Tan et al., 2013)	yes	yes	yes	yes	yes	yes	no

(Subirà et al., 2013)	yes	yes	yes	yes	yes	yes	yes
(Tang et al., 2013)	yes	yes	yes	yes	yes	yes	yes
(Hashimoto et al., 2014)	yes	yes	yes	yes	yes	yes	yes
(Spalletta et al., 2014)	yes	yes	yes	yes	yes	yes	yes
(Okada et al., 2015)	yes	yes	yes	yes	no	yes	no
(Kim et al., 2015b)	yes	yes	yes	no	yes	yes	yes
(Tang et al., 2015)	yes	yes	yes	yes	yes	yes	no
(Jayarajan et al., 2015)	yes	yes	yes	yes	yes	yes	yes

Abbreviations: BG, basal ganglia; GMV, grey matter volume; L, left; OCD, obsessive compulsive disorder; R, right

Table 4.11 Results of the reliability (jackknife) analyses for areas showing decreased activation during inhibitory control in ASD patients relative to healthy controls

	r/d ACC/MPFC	L DLPFC	R VLPFC/ anterior insula	L cerebellum (vermis)	L IPL	R MFG/ premotor
Study	0,32,22	-44,34,26	44,20,0	-12,-46,-10	-32,-52,54	40,14,50
(Schmitz et al., 2006)	yes	yes	yes	yes	yes	yes
(Kennedy et al., 2006)	yes	yes	yes	yes	yes	yes
(Kana et al., 2007)	yes	yes	yes	no	no	yes
(Shafritz et al., 2008)	yes	yes	yes	yes	no	yes
(Vaidya et al., 2011)	yes	yes	yes	yes	yes	yes
(Fan et al., 2012)	yes	yes	yes	yes	yes	yes
(Duerden et al., 2013)	yes	yes	yes	yes	yes	no
(Solomon et al., 2014)	yes	yes	yes	yes	yes	yes
(Chantiluke et al., 2015b)	yes	yes	yes	no	yes	no
(Ambrosino et al., 2014)	yes	yes	yes	yes	yes	yes
(Daly et al., 2014)	yes	yes	yes	yes	yes	yes
(Shafritz et al., 2015)	yes	yes	no	yes	yes	yes

Abbreviations: ASD, autism spectrum disorders; DLPFC, dorsolateral prefrontal cortex; IPL, inferior parietal lobe; L, left; MFG, middle frontal gyrus; r/d ACC/MPFC, rostral/dorsal anterior cingulate cortex/medial prefrontal cortex; R, right; VLPFC, ventrolateral prefrontal cortex

Table 4.12 Results of the reliability (jackknife) analyses for areas showing increased activation during inhibitory control in ASD patients relative to healthy controls

	Precuneus/PCC	R inf. temporal/occipital lobe	L mid. temporal gyrus
Study	-4,-40,54	38,-68,-12	-46,-54,6
(Schmitz et al., 2006)	no	yes	yes
(Kennedy et al., 2006)	no	yes	yes
(Kana et al., 2007)	yes	yes	yes
(Shafritz et al., 2008)	yes	yes	yes
(Vaidya et al., 2011)	yes	yes	yes
(Fan et al., 2012)	yes	yes	yes
(Duerden et al., 2013)	yes	yes	yes
(Solomon et al., 2014)	yes	yes	yes
(Chantiluke et al., 2015b)	yes	no	no
(Ambrosino et al., 2014)	yes	yes	yes
(Daly et al., 2014)	yes	yes	yes
(Shafritz et al., 2015)	yes	yes	yes

Abbreviations: ASD, autism spectrum disorders; inf., inferior; mid., middle; PCC, posterior cingulate cortex; R, right

Table 4.13 Results of the reliability (jackknife) analyses for areas showing decreased activation during inhibitory control in OCD patients relative to healthy controls.

Decreased activation in OCD versus healthy controls						
	v/r/d ACC/MPFC	R caudate	R cerebellum	R STL/mid. temporal gyrus	L postcentral gyrus	R PCC
Study	-2,26,42	14,8,14	30,-46,-16	44,-20,-10	-40,-16,38	-16,-38,38
(Nakao et al., 2005)	yes	yes	yes	yes	yes	yes
(Roth et al., 2007)	yes	yes	no	yes	yes	yes
(Yücel et al., 2007)	yes	yes	yes	yes	yes	yes
(Gu et al., 2008)	yes	yes	yes	no	no	no
(Woolley et al., 2008)	yes	yes	yes	yes	yes	yes
(Page et al., 2009)	yes	yes	yes	yes	yes	yes
(Fitzgerald et al., 2010)	yes	yes	yes	yes	yes	yes
(Britton et al., 2010)	yes	yes	yes	yes	yes	yes
(Schlösser et al., 2010)	yes	yes	yes	yes	yes	yes
(Huyser et al., 2011)	yes	yes	yes	yes	yes	yes
(Pena-Garijo et al., 2011)	yes	yes	yes	yes	yes	yes
(Kang et al., 2013)	yes	yes	no	yes	no	no
(Marsh et al., 2014)	yes	yes	yes	yes	no	no
(Morein-Zamir et al., 2015)	yes	yes	yes	yes	yes	yes

Abbreviations: L, left; mid., middle; OCD, obsessive compulsive disorder; PCC, posterior cingulate cortex; R, right; STL, superior temporal lobe; v/r/d ACC/MPFC, ventral/rostral/dorsal anterior cingulate cortex/medial prefrontal cortex

Table 4.14 Results of the reliability (jackknife) analyses for areas showing increased activation during inhibitory control in OCD patients relative to healthy controls

Increased activation in OCD versus healthy controls			
	L insula/putamen/premotor/precentral/VLPFC/STL	R premotor	L superior parietal
Study	-56,-4,6	36,-8,54	-18,-62,70
(Nakao et al., 2005)	yes	no	yes
(Roth et al., 2007)	yes	yes	yes
(Yücel et al., 2007)	no	no	yes
(Gu et al., 2008)	yes	yes	yes
(Woolley et al., 2008)	yes	yes	yes
(Page et al., 2009)	yes	yes	yes
(Fitzgerald et al., 2010)	yes	yes	yes
(Britton et al., 2010)	yes	yes	yes
(Schlösser et al., 2010)	yes	yes	yes
(Huyser et al., 2011)	yes	yes	yes
(Pena-Garijo et al., 2011)	yes	yes	yes
(Kang et al., 2013)	yes	yes	no
(Marsh et al., 2014)	yes	yes	no
(Morein-Zamir et al., 2015)	yes	yes	yes

Abbreviations: L, left; OCD, obsessive compulsive disorder; R, right; STL, superior temporal lobe; VLPFC, ventrolateral prefrontal cortex

CHAPTER 5 - DISORDER-SPECIFIC AND SHARED BRAIN ABNORMALITIES DURING VIGILANCE IN AUTISM AND OBSESSIVE-COMPULSIVE DISORDER

This chapter is presented as the final accepted manuscript version of the published peer-reviewed journal article:

Carlisi, CO, Norman, LJ, Murphy, CM, Christakou, A, Chantiluke, K, Giampietro, V, Simmons, A, Brammer, M, Murphy, DG, MRC AIMS Consortium, Mataix-Cols, D, Rubia, K. Disorder-specific and shared brain abnormalities during vigilance in autism and obsessive-compulsive disorder, *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, (2016).

Advanced online publication: December 31, 2016.

DOI: http://dx.doi.org/10.1016/j.bpsc.2016.12.005

Additional details not originally included in the published manuscripts regarding participant assessment and questionnaire measures are described at length in Appendix A. This information applies to Chapters 5, 6 and 7 of this thesis.

5.1 Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by social and communication difficulties and stereotyped, repetitive behaviours (American Psychiatric Association, 2013) with a prevalence of 0.6-2.0%, predominantly in males (Blumberg et al., 2013). Obsessive-compulsive disorder (OCD) is characterized by recurrent, intrusive and distressing thoughts (obsessions) and repetitive behaviours (compulsions) (American Psychiatric Association, 2013), affecting 1-3% of the population with a higher prevalence in males among paediatric samples (Ruscio et al., 2010). Rates of comorbidity of OCD in autistic children have

been estimated to be as high as 37% (Leyfer et al., 2006). Conversely, estimates of ASD rates in OCD patients are lower, around 6% (Ivarsson and Melin, 2008, Murray et al., 2015). Clinically, compulsions in OCD are sometimes difficult to separate from repetitive behaviours in ASD. Both disorders also commonly present with inattention and even ADHD, which may in some cases contribute to respective phenotypes including attention problems (van der Meer et al., 2012, Brem et al., 2014). These overlaps have been attributed to shared genetic risk and biological mechanisms, and diagnostic mislabelling (Russell et al., 2016), highlighting a need to improve understanding of the underlying neural mechanisms to disentangle comorbidity between the disorders and identify novel biomarkers and treatment targets (Cadman et al., 2015).

Vigilance incorporates sustained attention, or the ability to maintain focus toward infrequently occurring stimuli (Parasuraman and Yantis, 1998), and focused attention, or the ability to concentrate on one stimulus while excluding the influence of others (Benzina et al., 2016). There is evidence for deficits in vigilance and sustained attention in ASD (Murphy et al., 2014, Chien et al., 2015), albeit with some negative findings (Johnson et al., 2007). In OCD some studies support attention deficits across various domains (focused attention, sustained attention, selective attention, attention span, information processing) relative to controls (Nakao et al., 2014, Shin et al., 2014, Koch and Exner, 2015), while other studies found no deficits (Abramovitch et al., 2015a, Martoni et al., 2015). However, focused attention is perhaps the most widely studied attention domain in OCD, and the majority of studies support focused attention deficits (Benzina et al., 2016). Attentional priority to obsessions is a key feature of OCD, and OCD individuals have shown self-reported impaired attentional control (Armstrong et al., 2011). Thus, impairments in focused and sustained attention seemingly fit with clinical characteristics of the disorder and have been supported by the

neuropsychological literature (Benzina et al., 2016). Discrepancy is likely due to heterogeneous samples and tasks.

On cognitive and symptom-based measures, ASD has been related to inattention. Thus ASD can be characterised by short attention span, and impulsivity and inattention symptoms are common (Corbett and Constantine, 2006). Furthermore, ASD individuals are typically impaired on neurocognitive measures of sustained and selective attention (van der Meer et al., 2012). There is evidence for fronto-striatal, parietal and cerebellar abnormalities in ASD during selective and flexible attention (Schmitz et al., 2006, Shafritz et al., 2008). Specifically, hypoactivity has been observed in ASD in middle-frontal gyrus, caudate and anterior cingulate cortex (ACC) (Fan et al., 2012). However, only two fMRI studies have measured sustained attention in ASD, one in adolescents (Christakou et al., 2013b) and one in a combined sample of adolescents and adults (Murphy et al., 2014). These investigations found that ASD individuals exhibited decreased activation in left dorsolateral-prefrontal striato-thalamic and parietal regions but increased activation in the cerebellum, presumably compensating for frontal hypoactivation, and in precuneus, reflecting poor deactivation of the default mode network linked to increased mind-wandering (Christakou et al., 2013b). The first cross-sectional fMRI developmental investigation of sustained attention in ASD found that controls, but not ASD individuals, had enhanced activation in inferior and dorsolateral-prefrontal, striatal, temporal and cerebellar regions with age, suggesting abnormal functional maturation of attention networks in ASD (Murphy et al., 2014).

Clinical symptoms of inattention have been reported especially in paediatric OCD patients (Abramovitch et al., 2015b), and OCD patients have shown deficits in selective and focused attention (Benzina et al., 2016). Paediatric and adult studies of OCD across various cognitive domains have suggested that the disorder is characterized

by dysfunctional attention networks involving basal ganglia (BG) and medial and orbitofronto-striatal regions (Nakao et al., 2014). However, there is also evidence that abnormalities may additionally be driven by dysfunctional temporo-parietal and cerebellar networks (Chamberlain et al., 2005, Menzies et al., 2008), supporting phenotypes of distracted focused attention to external stimuli and inability to disengage from obsessions. Specifically, OCD patients exhibit hypoactivation in lateral-prefrontal cortex (PFC), medial-orbitofrontal cortex (OFC) and caudate but increased activation in ventrolateral PFC and ACC during selective and other attention-based tasks (Rubia et al., 2011, Shin et al., 2014), suggesting top-down ventrolateral PFC and ACC control over striatal underactivation. However, no fMRI studies have examined vigilance in OCD or compared ASD and OCD.

Given diagnostic overlap and potential aetiological links between ASD and OCD, it is critical to understand neurofunctional mechanisms that are shared/unique between these disorders. Work has begun to focus on delineating neural mechanisms between these disorders (see Chapter 4; (Carlisi et al., 2016b)), but a comparison in the context of attention is lacking. Despite a dearth of robust neurocognitive associations between attention problems and these disorders, investigating this domain in ASD and OCD may be useful for pinpointing differences/similarities in associated brain networks giving rise to clinical phenotypes in each disorder. Thus, this study compared brain function of boys with ASD, OCD and typically developing controls during a parametrically modulated fMRI vigilance task with increasing sustained attention loads. fMRI investigations of psychomotor vigilance using other paradigms (e.g. continuous performance test) in healthy adolescents and adults showed activation in inferior and dorsolateral-prefrontal, striato-thalamic, parieto-temporal and cerebellar regions (Rubia et al., 2009c, Smith et al., 2011). Therefore, we hypothesized that both disorders would show underactivation in inferior-frontal and dorsolateral-prefronto-striato-cerebellar

sustained attention networks relative to controls and that this effect would be more pronounced with increasing attention load.

5.2 Methods and materials

5.2.1 Participants

Sixty right-handed (Oldfield, 1971) boys (twenty typically-developing controls, twenty boys with ASD, twenty boys with OCD) 11-17 years, IQ≥70 (Wechsler, 1999) were included. ASD diagnosis was made by a psychiatrist using ICD-10 criteria (WHO, 1992) and confirmed with the Autism Diagnostic Interview-Revised (ADI-R; (Lord et al., 1994)). The Autism Diagnostic Observation Schedule (ADOS; (Lord et al., 2000)) was also completed; all ASD boys reached cut-offs for autism in all domains of the ADI-R and ADOS. Based on the structured interview, comorbidity with other disorders including OCD was excluded by a consultant psychiatrist. Parents also completed the Social Communication Questionnaire (SCQ; (Rutter et al., 2003)) and the Strengths and Difficulties Questionnaire (SDQ; (Goodman and Scott, 1999))(see Supplementary Information, section 5.6). ASD participants had a physical examination to exclude medical disorders and biochemical, hematological and chromosomal abnormalities associated with ASD. All ASD boys were medication-naïve.

Twenty boys with OCD were recruited from a National & Specialist OCD clinic at the Maudsley Hospital. OCD diagnosis was made by a psychiatrist/clinical psychologist in accordance with ICD-10 criteria after an in-depth, semi-structured interview between patient and clinician was used to administer an expanded version of the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS; (Goodman et al., 1989)). Absence of comorbidity, including ASD, was confirmed by a consultant psychiatrist after administration of the structured CY-BOCS interview. Parents

completed the SDQ. Four OCD boys were prescribed stable doses of selective serotonin reuptake inhibitors (SSRIs; see Supplementary Information, section 5.6).

Twenty healthy age and handedness-matched controls were recruited by advertisement and initially screened over the phone for the current or lifetime presence of any exclusion criteria including comorbidity. Controls scored below clinical cut-offs on the SDQ and SCQ and had no history of any psychiatric or physical comorbidity.

Exclusion criteria included comorbid psychiatric disorders, medical disorders affecting brain development, drug/alcohol dependency, head injury, genetic conditions associated with ASD, abnormal brain structural MRI findings and MRI contraindications. Thirty-one participants (fifteen controls, sixteen ASD) also participated in our fMRI studies of sustained attention in ASD vs. ADHD (Christakou et al., 2013b) and functional maturation of sustained attention networks in ASD vs. controls (Murphy et al., 2014). Some participants participated in other fMRI tasks during their visit, data from which are published elsewhere (Chantiluke et al., 2014a, Chantiluke et al., 2014b, Chantiluke et al., 2015a, Chantiluke et al., 2015b).

The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the local Research Ethics Committee (05/Q0706/275). Study details were explained to child and guardian, and written informed consent was obtained for all participants.

5.2.2 Psychomotor vigilance task

Subjects practiced the task briefly in a mock scanner. The 12-minute task (Murphy et al., 2014) is an adapted variant of psychomotor vigilance and delay tasks (Rubia et al., 1998, Drummond et al., 2005) requiring sustained and focused attention (Figure 5.1). Subjects responded as quickly as possible within 1-second via a right-

handed button press upon presentation of a timer counting up in milliseconds from zero. A premature response was recorded if the button was pressed before timer presentation. The timer appeared after short, predictable delays of 0.5s in series of 3-5 stimuli (260 total), or after an unpredictable delay of 2, 5 or 8s (20/each), pseudo-randomly interspersed into blocks after 3-5 delays of 0.5s. The 0.5s delays are typically anticipated, placing a larger demand on sensorimotor synchronization (Miyake et al., 2004), while the longer, infrequent delays place a higher load on sustained attention/vigilance.

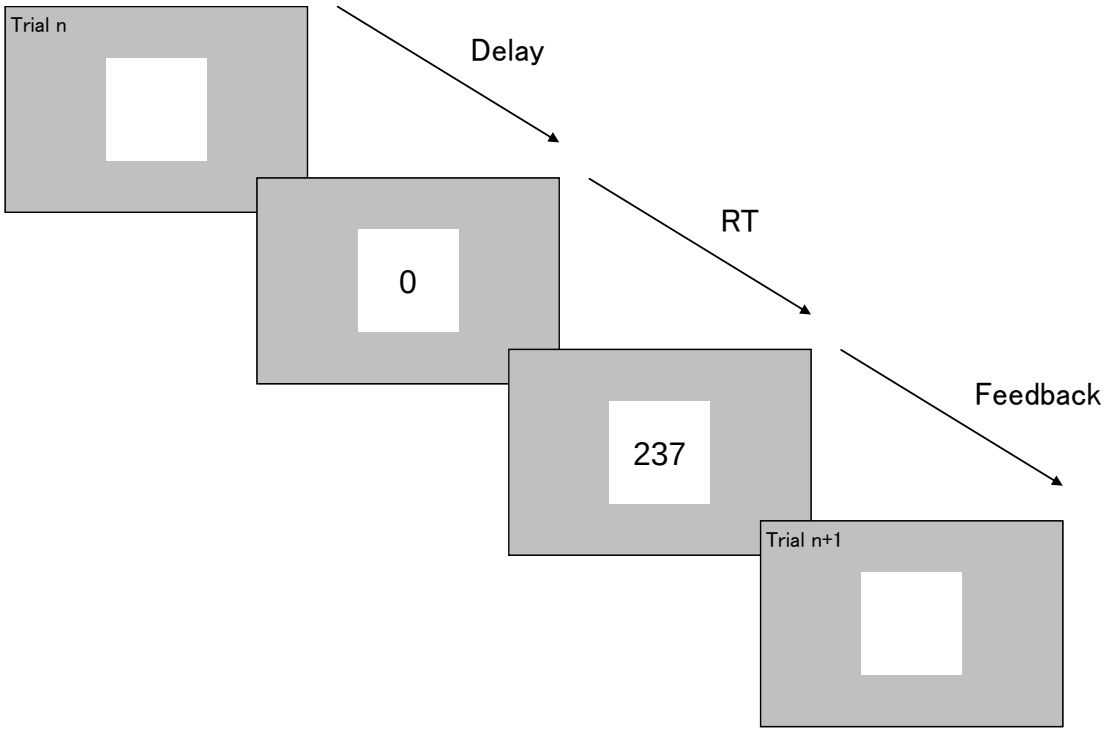


Figure 5.1 Psychomotor vigilance task

After a variable delay of 500, 2000, 5000 or 8000ms, a counter appeared on the screen, counting up from 0 in milliseconds. Subjects had to respond as quickly as possible to stop the counter by pressing a button with their right index finger.

5.2.3 Analysis of performance

Univariate repeated-measures ANOVAs with group as between-subject factor and delay (2/5/8s) as within-subject repeated measure examined group differences and delay effects on mean reaction time (MRT), intrasubject response variability (standard deviation) of RT (SDintrasubject), and omission errors.

5.2.4 fMRI acquisition

Gradient-echo echo-planar MR imaging (EPI) data were acquired on a 3T General Electric Signa HDx Twinspeed scanner (Milwaukee, WI) using a quadrature birdcage head coil. In each of 22 non-contiguous planes parallel to the anterior-posterior commissure, 480 T_2*-weighted images depicting blood-oxygenation-level-dependent (BOLD) contrast spanning the whole brain were acquired (TE=30ms; TR=1.5s; flip angle=60^o; in-plane resolution=3.75mm; slice-thickness=5.0mm; slice-skip=0.5mm). A whole-brain high-resolution structural scan (inversion recovery gradient EPI) on which to superimpose the activation maps was also acquired in the inter-commissural plane (TE=40ms; TR=3s; flip angle=90^o; slices=43; slice-thickness=3.0mm; slice-skip=0.3mm) providing complete brain coverage.

5.2.5 fMRI analysis

Event-related activation data were acquired in randomized trial presentation and analysed using non-parametric methods (XBAMv4.1, www.brainmap.co.uk (Brammer et al., 1997, Bullmore et al., 1999b)). XBAM makes no normality assumptions, uses median statistics to control outlier effects, and permutation testing, giving excellent type-I error control (Thirion et al., 2007). After pre-processing, time-series analysis for individual subjects was based on published wavelet-based data resampling methods for

fMRI data (see Supplementary Information, section 5.6) (Bullmore et al., 1999b, Bullmore et al., 2001).

For between-group comparisons, a 3x3 split-plot ANOVA (3 delays, 3 groups) tested for group, delay and group-by-delay interaction effects using a randomisation-based test for voxel or cluster-wise differences (Bullmore et al., 1999b). Less than 1 false positive activation cluster was expected at $p<0.05$ (voxel-level) and $p<0.01$ (cluster-level). Statistical measures of BOLD response for each participant were then extracted in each significant cluster and *post-hoc t*-tests were conducted to identify between-group differences.

5.2.6 Influence of behaviour, symptoms and medication

To examine whether activation in regions showing a group-by-delay interaction was related to clinical symptoms or task performance, we extracted statistical BOLD responses for the longest delay (the delay with the largest group-effect) from these clusters and correlated this (Spearman two-tailed) with MRT and SDintrasubject within each group. Within diagnostic groups, we correlated BOLD responses from clusters that were abnormal relative to controls (e.g. cerebellum/occipital in both groups and the other three clusters in OCD-see results) with disorder-relevant symptom measures, ADOS social/communication sub-scales for ASD and CY-BOCS scores for OCD.

To test for medication effects on activation for the OCD boys prescribed SSRIs, analyses were repeated covarying for medication status and excluding medicated participants.

5.3 Results

5.3.1 Participants

Groups did not differ on age or IQ (Table 5.1). As expected, groups differed on total and sub-scores of the SDQ. *Post-hoc* tests showed that on total and peer-relations subscales, all patients were impaired relative to controls, but ASD boys were more severely impaired than OCD boys (total: all $p<0.001$; peer: all $p<0.05$). On emotional subscales, both diagnostic groups were impaired relative to controls ($p<0.001$) but did not differ from each other. On prosocial and hyperactivity/inattention subscales, ASD boys were impaired relative to controls and OCD boys ($p<0.001$), who did not differ from controls. On the conduct problems subscale, only ASD boys differed from controls ($p<0.005$).

Table 5.1 Participant characteristics for healthy control boys and boys with ASD or OCD

Variables	HC (N=20) Mean (SD)	ASD (N=20) Mean (SD)	OCD (N=20) Mean (SD)	*F* test (DF)	*p* value
Age (years)	15.1 (2.0)	15.2 (1.3)	15.7 (1.4)	0.9 (2,57)	0.43
IQ	119.7 (11.9)	112.2 (14.4)	117.7 (13.4)	1.7 (2,57)	0.19
SCQ total score	2.32 (2.3)	18.66 (8.1)	-	77.0 (1,47)	<0.001
SDQ total score	5.6 (4.2)	19.7 (6.8)	12.5 (5.6)	35.6 (2,66)	< 0.001
SDQ emotional distress subscale	0.9 (1.8)	4.4 (2.9)	4.4 (2.6)	13.1 (2,66)	< 0.001
SDQ conduct subscale	0.9 (1.1)	2.7 (2.2)	1.9 (1.5)	6.6 (2,66)	0.003
SDQ peer relations subscale	1.5 (1.7)	6.6 (2.3)	3.3 (3.0)	28.7 (2,66)	< 0.001
SDQ hyperactive impulsive/inattentive subscale	2.7 (2.4)	5.9 (2.6)	3.0 (2.7)	12.5 (2,66)	< 0.001
SDQ prosocial behaviour subscale	8.4 (2.4)	4.4 (2.4)	7.7 (2.6)	18.6 (2,66)	< 0.001
ADOS communication score	-	3.6 (1.2)	-	-	-
ADOS social interaction score	-	9.0 (2.3)	-	-	-
ADOS communication+social	-	12.7 (3.1)	-	-	-
ADOS stereotypy score	-	1.5 (1.5)	-	-	-
ADI communication score	-	16.6 (4.7)	-	-	-
ADI social interaction score	-	20.0 (5.3)	-	-	-
ADI repetitive behaviour score	-	6.5 (2.4)	-	-	-
CY-BOCS total score	-	-	22.3 (5.8)	-	-
CY-BOCS – obsessions	-	-	10.8 (3.6)	-	-
CY-BOCS – compulsions	-	-	12.0 (3.1)	-	-

Abbreviations: ADI, Autism diagnostic interview; ADOS, Autism diagnostic observation schedule; ASD, Autism Spectrum Disorder; CYBOCS, Children's Yale-Brown Obsessive-Compulsive Scale; HC, healthy controls; OCD, obsessive-compulsive disorder; SCQ, social communication questionnaire; SDQ, strengths and difficulties questionnaire

5.3.2 Performance data

Repeated-measures ANOVAs showed no significant within-subjects effect of delay on MRT [$F(1.7,95.1)=1.99$, $p=0.15$], SDintrasubject [$F(2,114)=0.56$, $p=0.57$], or omissions [$F(1.7,98.8)=0.48$, $p=0.59$].

There was no significant group-effect on MRT [$F(2,57)=1.5$, $p=0.23$], SDintrasubject [$F(2,57)=0.78$, $p=0.46$] or omissions [$F(2,57)=1.00$, $p=0.37$].

There was no significant group-by-delay interaction effect for MRT [$F(3.3,95.1)=0.77$, $p=0.53$], SDintrasubject [$F(4,114)=1.71$, $p=0.15$], or omissions [$F(3.5,98.8)=1.82$, $p=0.14$](Table 5.3).

5.3.3 Movement

Groups did not differ on minimum [$F(2,57)=1.0$, $p=0.38$], maximum [$F(2,57)=0.3$, $p=0.76$], or mean [$F(2,57)=0.003$, $p=1.00$] head translation in 3D-Euclidian space.

5.3.4 Group maps of brain activation

Images of within-group brain activation for each delay (2/5/8s) contrasted against 0.5s trials are described in the Supplementary Information, section 5.6 (Figure 5.4).

5.3.5 Delay effect

All subjects showed distributed activation with increasing delay in a bilateral network comprising ventromedial/dorsolateral/inferior PFC, anterior/posterior cingulate, BG supplementary motor area, temporo-parietal and cerebellar regions and

thalamus and hippocampal gyri (see Supplementary Information section 5.6, Figure 5.5).

5.3.6 Group effect

Split-plot ANOVA revealed significant group-effects in left insula/inferior frontal gyrus (IFG) extending into pre/postcentral gyrus/superior temporal lobe (STL) and right posterior cingulate cortex (PCC)/STL extending into middle temporal lobe (MTL)/occipital lobe (Figure 5.2; Table 5.2A).

Post-hoc analyses showed OCD boys had decreased activation in left insula/IFG relative to controls ($p<0.001$) and ASD boys ($p=0.002$), who did not differ from controls, and in right PCC/STL relative to controls ($p=0.002$) and ASD boys ($p=0.001$) who did not differ from controls.

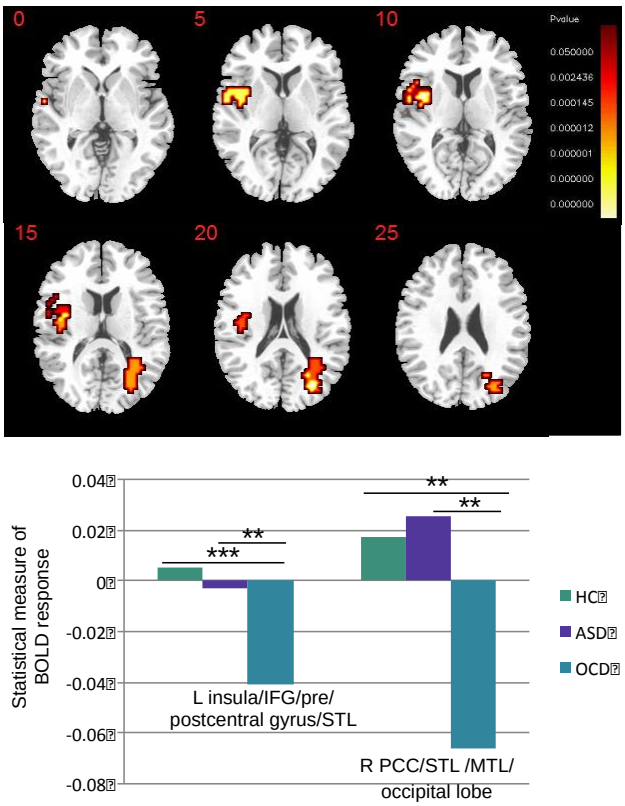


Figure 5.2 Between-group differences in brain activation between healthy control boys, boys with Autism Spectrum Disorder (ASD) and boys with Obsessive-Compulsive Disorder (OCD)

Analysis of variance (ANOVA) showing the main effect of group on brain activation for all delays (2s, 5s, 8s) combined, contrasted against 0.5s trials. Talairach z-coordinates are shown for slice distance (in mm) from the intercommissural line. The right side corresponds with the right side of the brain. **indicates significant at $p<0.005$, ***indicates significant at $p<0.001$. See Appendix B for graphs including standard error bars.

Table 5.2 ANOVA effects for brain activation differences between boys with ASD, OCD and healthy controls

Subject contrast	Brain regions of activation	Brodmann areas	Peak Talairach coordinates (x,y,z)	Voxels	*p*-value
(A) Main effect of group					
OCD<HC,ASD	**L insula**/IFG/pre/ postcentral gyrus/STL	45/44/6/4/43/22	-40,0,-2	49	0.009
OCD<HC,ASD	**R PCC/STL**/MTL/ occipital lobe	23/31/22/39/19	29,-63,9	38	0.006
(B) Group x Delay interaction effects					
OCD<HC,ASD	**L insula**/IFG/precentral gyrus/STL/MTL	47/44/45/6/41/22/ 21	-43,11,-2	91	0.0008
OCD<HC,ASD	**L IPL**/pre/ postcentral gyrus	40/6/4/3/1	-51,-30,37	48	0.0009
OCD>ASD,HC	**rMPFC**/superior frontal/ACC	9/10/32	11,56,20	63	0.001
ASD,OCD>HC	**Cerebellar vermis**/occipital lobe/lingual gyrus	17/18/19	7,-70,-13	49	0.003

Abbreviations: ACC, anterior cingulate cortex; ANOVA, analysis of variance; ASD, autism spectrum disorder; HC, healthy controls; IFG, inferior frontal gyrus; IPL, inferior parietal lobe; MTL, middle temporal lobe; OCD, obsessive-compulsive disorder; PCC, posterior cingulate cortex; rMPFC, rostral medial prefrontal cortex; STL, superior temporal lobe. **Bold regions** indicate cluster peak

5.3.7 Group-by-delay effects

Split-plot ANOVA showed significant group-by-delay interaction effects in four clusters, one of which overlapped with observed results in the group-effect analysis: left insula/IFG extending into precentral gyrus/STL/MTL, left inferior parietal lobe(IPL)/pre/postcentral gyrus, rostromedial-prefrontal cortex (rMPFC)/superior frontal gyrus/anterior cingulate cortex (ACC), and cerebellar vermis/occipital lobe/lingual gyrus (Figure 5.3; Table 5.2B).

Post-hoc analyses showed that in left IFG/insula (Figure 5.3A) and left IPL/pre/post-central gyrus (Figure 5.3B), OCD boys had progressively reduced activation with increasing delay ($p<0.005$) relative to ASD boys and controls ($p<0.005$), who did not differ and who's activation in this region did not change with delay. In rMPFC (Figure 5.3C), OCD boys had increased activation with increasing delay ($p<0.004$). There was no between-group difference in the 2s condition, but for 5s and 8s, OCD boys had increased activation relative to ASD boys and controls ($p<0.005$), who did not differ and whose activation in this region did not change with delay. In cerebellum/occipital lobe (Figure 5.3D), both diagnostic groups had increased activation with increasing delay (ASD: $p<0.05$; OCD: $p<0.005$) and shared enhanced activation in all delays relative to controls (ASD vs. C: $p<0.04$; OCD vs. HC: $p<0.001$).

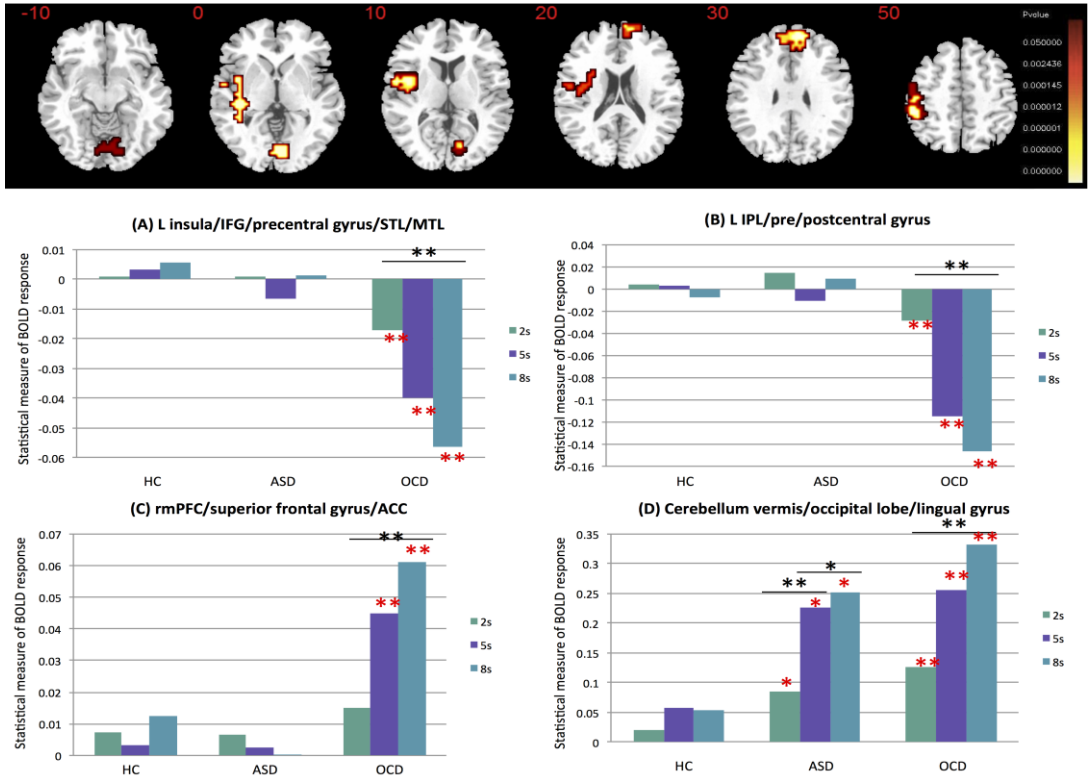


Figure 5.3 Group x Delay interaction between healthy control boys, boys with Autism Spectrum Disorder (ASD) and boys with Obsessive-Compulsive Disorder (OCD) and delay condition (2s, 5s, 8s)

Analysis of variance (ANOVA) showing group-by-delay interaction effects on brain activation. Talairach z-coordinates are shown for slice distance (in mm) from the intercommissural line. The right side corresponds with the right side of the brain. Red asterisks indicate significant difference between diagnostic group and controls. Black asterisks indicate significant difference within group between conditions. *indicates significance at $p<0.05$, **indicates significance at $p<0.005$. See Appendix B for graphs including standard error bars.

5.3.8 Influence of performance, clinical symptoms and medication

Within patients, there were no significant correlations between clinical measures and brain activation. There was no relationship between performance and activation within any of the three groups.

When medication was covaried, results remained unchanged, suggesting that medication did not significantly affect activation differences observed during the task. When analyses were repeated excluding these four patients, findings were still observed at a more lenient significant threshold of $p<0.05$, likely as an effect of reduced power to detect group-differences.

5.4 Discussion

This is the first fMRI study to directly compare boys with ASD and OCD to investigate shared/disorder-specific abnormalities in brain function and the first to make this comparison using sustained attention. During a parametrically-modulated vigilance task, OCD boys had disorder-specific patterns of reduced activation in left lateral-fronto-parieto-temporal regions but enhanced activation in medial frontal regions with increasing task-difficulty relative to controls and ASD boys, who did not differ from one another. Both disorders shared enhanced activation relative to controls with increasing delay in cerebellum/occipital lobe.

Neither diagnostic group differed from controls on task performance (MRT, SDintrasubject). Across all groups, participants activated distributed ventromedial, dorsolateral and inferior-prefronto-striato-thalamic and temporo-parietal networks with increasing attention load, suggesting the task elicited the expected brain response, as dorsolateral and inferior-fronto-striato-temporo-parietal networks are important for maintaining attention (Rubia et al., 2009c, Christakou et al., 2013b).

OCD boys had disorder-specific activation decreases relative to controls and ASD boys in left insula, IFG and STL, which furthermore showed decreases in activation as a function of increasing attention load in OCD but not the other groups. The insula is involved in saliency detection and timing functions (Voisin et al., 2006, Wiener et al., 2010). Reduced insular and paralimbic activation presumably reflects these regions' role in motivation control which may influence attention (Menon and Uddin, 2010). Thus, OCD-specific deactivation in this region may be a disorder-specific signature, shifting cognitive resources away from internal thoughts to elicit task-relevant attention comparable to controls. The insula is furthermore involved in switching between task-related central-executive networks and task-unrelated "default mode" network activations, suggesting that the insula facilitates 'dampening down' of default mode activity during sustained attention (Langner and Eickhoff, 2013). Thus, OCD-specific decreased insula activation with increasing attention load could relate clinically to difficulty maintaining attention toward task-relevant stimuli due to attentional priority to task-unrelated internally generated obsessions.

Left IFG is a key part of the ventral attention network and, along with lateral temporo-parietal regions, is important for attention orienting maintenance (Corbetta and Shulman, 2002). Investigations of ventral sustained attention systems generally implicate right-hemispheric regions (Corbetta et al., 2008, Langner and Eickhoff, 2013) (however, see (Vossel et al., 2014) for evidence of left-hemispheric activation). It is conceivable that observed left-hemisphere activation reflects sensorimotor effects of the right-handed button-press. This particular vigilance task has shown in previous studies (Christakou et al., 2013b, Murphy et al., 2014) to elicit predominantly left-lateralized activation in fronto-insular regions in healthy adults and children, supported by our within-group findings of predominantly left hemispheric fronto-insular activation presented in the Supplementary Information, section 5.6. Moreover, this effect could be

due to this region's role in motor timing and sensorimotor synchronization (Wiener et al., 2010). There have been age-related findings of increased IFG/insula activation during sustained attention and cognitive control between childhood and adulthood (Christakou et al., 2009b, Smith et al., 2011), suggesting abnormal functional maturation in OCD relative to ASD and controls, in line with structural MRI studies showing abnormal white matter development (Gonçalves et al., 2015) and decreased cortical thickness in adults with OCD relative to controls (Fouche et al., 2016). Taken together, this evidence suggests that abnormal inferior-frontal functional maturation may be a potential biomarker for OCD.

OCD boys also had disorder-specific decreased activation in inferior-parietal and superior and middle-temporal regions with increasing attention load relative to controls and ASD. Inferior parietal/superior temporal lobes show decreased activation as a function of time during vigilance in healthy individuals (Breckel et al., 2011), suggesting this effect may be exaggerated in OCD, particularly as the effect was more pronounced with increasing delays. Similar reductions in inferior-fronto-parieto-cerebellar vigilance and motivation networks have been found during sustained attention in ADHD adolescents (Rubia et al., 2009b, Christakou et al., 2013b, Hart et al., 2013), suggesting abnormalities may represent underlying mechanisms of inattention that are disorder-specific to OCD vs. ASD. Interestingly, our previous study comparing vigilance in ASD and ADHD (Christakou et al., 2013b) found reduced left dorsolateral-prefrontal activation in younger ASD subjects relative to controls, but these findings were based on a comparison of ASD to ADHD participants not included in the present study, potentially reflecting age-related differences.

Inferior parietal and temporal regions are involved in attentional orienting to time and readjustment of attention after disengagement (Corbetta et al., 2008). Thus, reduced activation in this region with increasing delay in OCD but not ASD could

suggest that sustained attention is more neurofunctionally impaired in OCD than ASD, particularly during increasing attention load. This may be related clinically to a poor ability to re-engage with task-relevant attention in OCD individuals if they become distracted by intrusive thoughts.

While OCD participants showed disorder-specific patterns of progressively decreased activation with increasing attention load in lateral fronto-parieto-temporal regions, they also showed progressively increased activation in medial frontal ACC/MPFC relative to ASD boys and controls. MPFC/ACC hyperactivation is a classic pattern in OCD during attention-based tasks (Chamberlain et al., 2005), particularly in the context of error monitoring (Menzies et al., 2008). Anterior mPFC has been implicated in withholding pre-planned responses and seems to facilitate action intention across delays (Haynes et al., 2007). Moreover, this region may down-regulate motor activity, acting as a control mechanism inhibiting response until target presentation (Danielmeier et al., 2011). Thus, increased MPFC activation in OCD with increasing attention load as left lateral fronto-temporo-parietal activation decreased could reflect compensation to elicit behaviour similar to controls and ASD boys.

Taken together, OCD-specific findings of reduced left inferior-frontal and temporo-parietal but increased MPFC/ACC activation relative to controls is in line with common patterns of reduced lateral fronto-temporo-parietal activation/morphology in OCD but increased function/morphology in MPFC during inhibition, error monitoring and symptom provocation (Radua et al., 2010, Norman et al., 2016) (and see Chapter 4; (Carlisi et al., 2016b)). The present findings extend this evidence to attention and vigilance, suggesting this pattern may be more characteristic of OCD pathophysiology.

Both disorders shared increased activation in cerebellar vermis/lingual gyrus with increasing delays relative to controls. The cerebellum is implicated in the

pathophysiology of ASD (Allen and Courchesne, 2003) and OCD (van den Heuvel et al., 2009). In ASD, this fits with enhanced cerebellar vermis activation relative to controls and ADHD individuals during sustained attention (Christakou et al., 2013b) and may be associated with structural deficits (Stigler et al., 2011) and abnormal fronto-cerebellar connectivity in ASD (Minshew and Williams, 2007). Moreover, the cerebellum has been implicated in attention to time intervals (Coull, 1998), suggesting that ASD and OCD share deficits in this aspect of attention orienting involved in vigilance to temporal delay. A recent fMRI meta-analysis of sustained attention (Langner and Eickhoff, 2013) found that the cerebellar vermis is activated with increasing delays, suggesting its role in timing and anticipation of motor responses, in line with findings of impaired anticipatory timing in cerebellar lesion patients (Diedrichsen et al., 2005). Abnormalities in the lingual gyrus have been linked to impaired sustained attention in depression (Yang et al., 2015). The present results extend this finding to OCD, suggesting that posterior regions are implicated in circuitry relevant to vigilance/attention and impaired in clinical populations associated with internal thought and rumination. The finding of progressively increased activation in this region in OCD boys relative to controls may compensate for neurofunctional impairments in OCD in left lateral inferior-fronto-temporo-parietal attention-related regions, leading to preserved task performance in this group.

Interestingly, while neither disorder showed performance deficits, there were shared and disorder-specific neurofunctional abnormalities for OCD relative to ASD. There are several explanations for this. Subject numbers required for fMRI studies are smaller than those required for neuropsychological analyses, reducing statistical power for behavioural analysis. Moreover, the aim of fMRI is to understand differences in neural networks between cases and controls during task performance. To relate activation differences to pathology and not simply to performance differences, it is

important that performance did not differ between groups (Rubia et al., 2010a). Across child/adult psychiatry, neurofunctional differences have been demonstrated between cases and controls despite comparable task performance (Dickstein et al., 2006, Schmitz et al., 2008, Woolley et al., 2008, Halari et al., 2009). Therefore, apparently similar task performance is achieved with different neural activation between groups, particularly in OCD boys, who showed disorder-specific patterns of decreased lateral inferior-fronto-temporal and increased medial-frontal activation. It is possible that the increased medial-frontal activation may be compensatory in response to reduced lateral inferior fronto-temporal activation, suggesting OCD patients relied less on lateral and posterior attention mechanisms and more on medial-prefrontal regions for task-performance. Conversely, both disorders achieved comparable performance to controls with increased cerebellar-occipital activation, which may reflect shared neurofunctional mechanisms of enhanced default-mode activity.

Despite these differences in brain activation, groups did not differ in performance. However, this is an advantage, as brain activation was therefore not confounded by performance differences. Brain activation is typically more sensitive than performance to detect differences between groups in these patient groups (e.g. (Fitzgerald et al., 2010, Duerden et al., 2013, Ambrosino et al., 2014, Marsh et al., 2014, Chantiluke et al., 2015b, Morein-Zamir et al., 2015)). There was furthermore no correlation between clinical measures or task-performance and activation. While the subject numbers have been shown to be sufficient for fMRI analyses (Thirion et al., 2007), the performance and correlation analyses, however, are underpowered which may explain the negative findings.

This study has several limitations. While patients with psychiatric comorbidities were excluded, we cannot rule out the presence of sub-threshold symptoms of other disorders such as ADHD. This is in line with the debate around comorbidity versus

overlapping phenotypes and their respective contribution to behaviour and clinical presentation, particularly in the context of ASD and ADHD (Corbett and Constantine, 2006). It would have been interesting to investigate correlations with more detailed attention-based behavioural questionnaires. Nevertheless, SDQ scores have been shown to strongly correlate with inattention symptoms on other measures such as the Child Behaviour Checklist (CBCL; (Achenbach, 1991)) (Goodman and Scott, 1999). Similarly, a standard OCD measure (e.g. CY-BOCS) was not administered to ASD patients. However, absence of OCD comorbidity in ASD individuals was confirmed by a psychiatrist based on a structured interview. A study strength is the inclusion of non-comorbid, medication-free ASD boys. However, four OCD boys were prescribed SSRIs. There is evidence for neurofunctional effects of serotonin (Murphy, 2010), but after covarying for and excluding medicated patients, findings remained (albeit at a slightly more lenient threshold), suggesting medication did not significantly affect brain function. Lastly, phenotypes of OCD are closely linked to anxiety (Mataix-Cols et al., 2004). While anxiety ratings were not collected before scanning, the possibility that OCD patients were more anxious compared to the other groups should not be discounted. This may partially explain the OCD group's reduced recruitment of attention-related brain regions and suggest that activation differences are indicative of anxiety as opposed to fundamental attention problems.

Future work could compare ASD individuals with and without co-morbid OCD to non-comorbid OCD individuals, building on this novel comparison to elucidate the mechanisms underlying clinical overlap of ASD and OCD. Moreover, it would be interesting to compare these patient groups with attention-related disorders such as ADHD to provide further insight into shared and/or disorder-specific neurofunctional attention mechanisms.

5.5 Conclusions

This study provides first evidence suggesting that OCD adolescents have disorder-specific abnormalities in sustained attention networks including left inferior and medial PFC and temporo-parietal regions relative to ASD, who had no frontal abnormalities. Findings suggest lateral inferior/medial-fronto-temporo-parietal abnormalities during sustained attention may be a distinct neural signature of OCD but not ASD. ASD and OCD individuals, however, shared abnormally enhanced activation in cerebellum/occipital lobe relative to controls. These results provide promising evidence for identification of biomarkers that may clarify underlying mechanisms driving sustained attention and respective symptom profiles in autism and OCD.

5.6 Supplementary information

As this chapter has been previously published, supplementary information is presented as available online, separate from the main text of Chapter 5:

DOI: http://dx.doi.org/10.1016/j.bpsc.2016.12.005

5.6.1 Supplementary methods

5.6.1.1 Participants

All but 3 ASD participants scored above clinical threshold for ASD on the Social Communication Questionnaire (SCQ; (Rutter et al., 2003)), but these patients were included on the basis of clinician-confirmed ASD diagnosis. Six ASD participants also scored above threshold for inattention/hyperactivity symptoms on the Strengths and Difficulties Questionnaire (SDQ; (Goodman and Scott, 1999)) but were not excluded on the basis that attention problems are common in ASD and clinician confirmation that ASD symptoms were the sole/primary clinical concern for these patients.

One OCD patient scored above clinical cut-off for inattention/hyperactivity symptoms on the SDQ but was not excluded on the basis that communication and attention difficulties can be misconstrued for OCD-related symptoms and the fact that no OCD patients met criteria for ASD or ADHD based on clinical interview.

5.6.1.2 OCD patient medication status

Patient 1: Sertraline 75mg

Patient 2: Sertraline 100mg

Patient 3: Sertraline 200mg

Patient 4: Fluvoxamine 100mg; risperidone 0.5mg

5.6.2 fMRI data analysis methods

5.6.2.1 Individual analysis

Data were first processed to minimize motion-related artefacts (Bullmore et al., 1999a). A 3-D volume consisting of the average intensity at each voxel over the entire experiment was calculated and used as a template. The 3D image volume at each time point was then realigned to this template by computing the combination of rotations (around the *x*, *y* and *z* axes) and translations (in *x*, *y* and *z*) that maximized the correlation between the image intensities and the volume in question and the template (rigid-body registration). Following realignment, data were then smoothed using a Gaussian filter (full-width at half-maximum (FWHM) 7.2 mm) to improve the signal-to-noise ratio of the images (Bullmore et al., 1999a). Following motion correction, global detrending and spin-excitation history correction, time series analysis for each subject was conducted based on a previously published wavelet-based resampling method for fMRI data (Bullmore et al., 1999b, Bullmore et al., 2001). At the individual-subject level, a standard general linear modelling approach was used to obtain estimates of the response size (beta) to each of the task conditions (2, 5 and 8s long delays) against an implicit baseline of 0.5s delays. We first convolved the main experimental conditions with 2 Poisson model functions (peaking at 4 and 8s). We then calculated the weighted sum of these 2 convolutions that gave the best fit (least-squares) to the time series at each voxel. A goodness-of-fit statistic (SSQ ratio) was then computed at each voxel consisting of the ration of the sum of squares of deviations from the mean intensity value due to the model (fitted time series) divided by that of the squares due to the residuals (original time series minus model time series). The appropriate null distribution for assessing significance of any given SSQ ratio was established using a wavelet-based data re-sampling method (Bullmore et al., 2001) and applying the model-fitting process to the resampled data. This process was repeated 20 times at each voxel

and the data combined over all voxels, resulting in 20 null parametric maps of SSQ ratios for each subject, which were combined to give the overall null distribution of SSQ ratio. This same permutation strategy was applied at each voxel to preserve spatial correlation structure in the data. Individual SSQ ratio maps were then transformed into standard space, first by rigid-body transformation of the fMRI data into a high-resolution inversion recovery image of the same subject, and then by affine transformation onto a Talairach template (Talairach and Tournoux, 1988).

5.6.2.2 Group analysis

For the group-level analysis, less than 1 false positive-activated 3D cluster was expected at $p<0.05$ (voxel-level) and $p<0.01$ (cluster-level). A group-level activation map was produced for each group and each experimental condition (2, 5 and 8s) by calculating the median observed SSQ ratios at each voxel in standard space across all subjects and testing them against the null distribution of median SSQ ratios computed from the identically transformed wavelet-resampled data (Brammer et al., 1997, Bullmore et al., 2001). The voxel-level threshold was first set to 0.05 and tests were conducted to identify voxels that might be plausibly activated followed by a test at a cluster-level threshold of $p<0.01$ to remove the false-positive clusters produced by the voxel-level test (Bullmore et al., 1999b, Bullmore et al., 2001). Next, a cluster-level threshold was computed for the resulting 3D voxel clusters. The necessary combination of voxel and cluster level thresholds was not assumed from theory but rather was determined by direct permutation for each dataset, giving excellent type-II error control (Bullmore et al., 1999b). Cluster mass rather than a cluster extent threshold was used to minimize discrimination against possible small, strongly responding foci of activation (Bullmore et al., 1999b).

5.6.3 Supplementary results

Table 5.3 Performance data

Performance measure, mean (SD)	Delay	Controls (N=20)	ASD boys (N=20)	OCD boys (N=20)
MRT (ms)	0.5s	300.31 (42.56)	294.12 (54.25)	300.04 (30.40)
	2s	379.24 (37.16)	404.74 (44.32)	392.99 (43.55)
	5s	378.29 (45.01)	398.55 (46.69)	388.29 (48.09)
	8s	386.87 (50.78)	411.60 (54.95)	388.66 (45.38)
SDintrasubject	0.5s	65.68 (25.33)	85.11 (31.10)	77.06 (30.53)
	2s	67.08 (29.75)	75.52 (37.26)	69.09 (23.00)
	5s	54.59 (23.21)	68.35 (31.40)	77.07 (38.10)
	8s	65.92 (23.93)	70.22 (32.05)	64.28 (31.59)
Omissions (number)	0.5s	0.60 (1.63)	0.58 (1.61)	0.45 (1.00)
	2s	0.15 (0.67)	0.05 (0.23)	0.00 (0.00)
	5s	0.20 (0.89)	0.05 (0.23)	0.00 (0.00)
	8s	0.30 (1.13)	0.00 (0.00)	0.00 (0.00)

Abbreviations: ASD, autism spectrum disorder; MRT, mean reaction time; ms, milliseconds; OCD, obsessive-compulsive disorder; s, seconds; SD, standard deviation

5.6.3.1 fMRI data – within-group activation results

Within each group separately (controls, patients with ASD, patients with OCD), all groups showed distributed increased activation with increasing delay in a widespread network encompassing bilateral cerebellum and occipital lobe, medial and superior temporal regions, posterior cingulate cortex, pre and post-central gyrus, insula and predominantly right dorsolateral prefrontal cortex extending into supplementary motor area as well as subcortical regions including bilateral thalamus and putamen. The OCD group (and controls to a lesser extent) also had increasing activation in dorsomedial prefrontal regions which was strongest in the 8s condition.

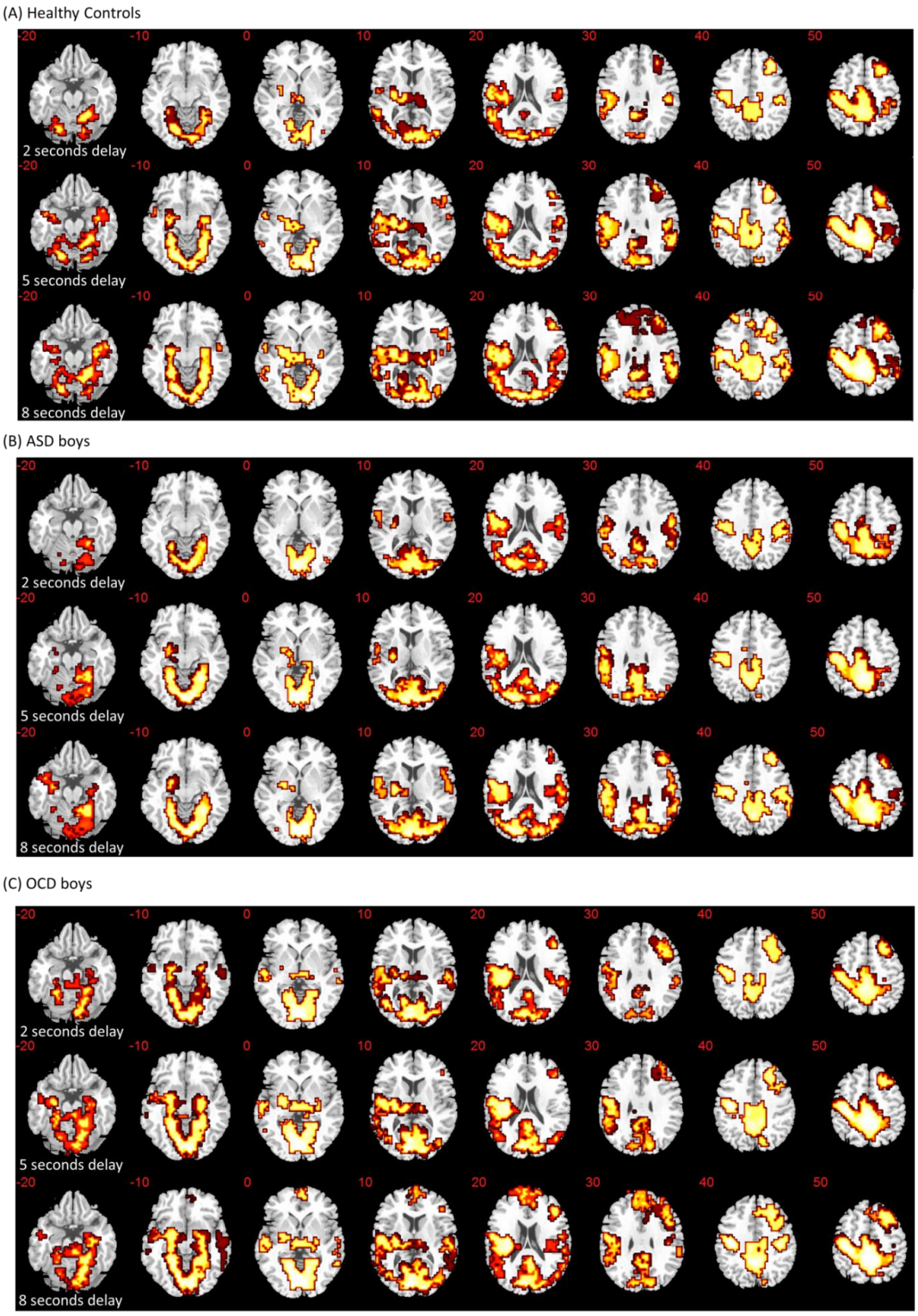


Figure 5.4 Within-group brain activation for each delay condition (2, 5, 8s)

Horizontal sections showing within-group brain activation for each delay condition of 2, 5 and 8 seconds for (A) healthy control boys, (B) boys with ASD and (C) boys with OCD. Talairach *z*-coordinates are shown for slice distance (in mm) from the intercommissural line. The right side of the image corresponds with the right side of the brain.

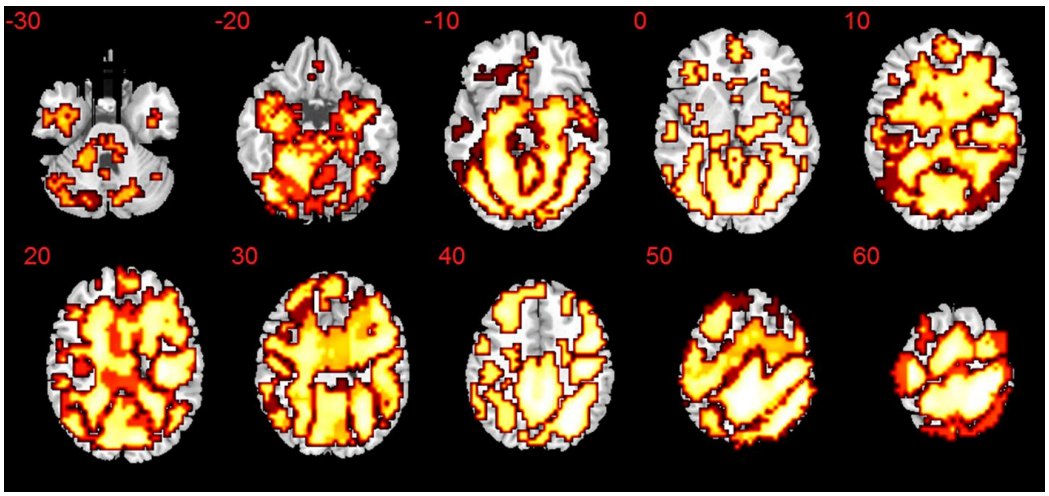


Figure 5.5 Main effect of delay across healthy controls, boys with ASD and boys with OCD

Horizontal sections showing brain activation across all groups (healthy controls, boys with ASD and boys with OCD) with increasing delay (2, 5 and 8 seconds). Talairach *z*-coordinates are shown for slice distance (in mm) from the intercommissural line. The right side of the image corresponds with the right side of the brain.

CHAPTER 6 - COMPARISON OF NEURAL SUBSTRATES OF TEMPORAL DISCOUNTING BETWEEN YOUTH WITH AUTISM SPECTRUM DISORDER AND WITH OBSESSIVE-COMPULSIVE DISORDER

This chapter is presented as the final author-submitted manuscript version of the journal article which has since been published, as this manuscript was under review at the time of writing. The submitted accompanying supplementary information has been re-incorporated as part of Chapter 6 of this thesis.

Reference: Carlisi, CO, Norman, LJ, Murphy, CM, Christakou, A, Chantiluke, K, Giampietro, V, Simmons, A, Brammer, M, Murphy, DG, MRC AIMS Consortium, Mataix-Cols, D, Rubia, K. Comparison of neural substrates of temporal discounting between youth with autism spectrum disorder and with obsessive-compulsive disorder, *Psychological Medicine* (2017). ePub ahead of print.

DOI: 10.1017/S0033291717001088

6.1 Introduction

Autism Spectrum Disorder (ASD) is characterized by social communication difficulties and stereotyped repetitive behaviours (American Psychiatric Association, 2013) with a prevalence of 0.6-2%, predominantly in males (Blumberg et al., 2013). Obsessive-Compulsive Disorder (OCD) is characterized by recurrent, intrusive and distressing thoughts (obsessions) and repetitive rituals (compulsions) (American Psychiatric Association, 2013), affecting 1-3% of the population with a higher male prevalence in paediatric samples (Ruscio et al., 2010). These disorders carry rates of comorbidity with one another exceeding 30% (Simonoff et al., 2008) and can sometimes be clinically difficult to separate (Doshi-Velez et al., 2014).

The allowance of co-diagnosis of OCD with ASD in DSM-5 questions whether cognitive phenotypes common to both disorders are mediated by shared or disorder-specific mechanisms. Converging evidence suggests repetitive behaviours in ASD and OCD may be mediated by shared mechanisms including behavioural disinhibition or motivation control (Hollander et al., 2007). Such impairments are thought to maintain diminished control over repetitive behaviours in ASD and compulsions in OCD and involve goal-directed reward-based decision-making. A meta-analysis of structural and functional neuroimaging studies comparing ASD and OCD found that both disorders share reduced structure and function during cognitive control in medial prefrontal regions but that OCD had disorder-specific increased function and structure in basal ganglia and insula while ASD had disorder-specific functional reduction in DLPFC and reduced PCC deactivation, presumably reflecting disorder-specific fronto-striato-insular dysregulation in OCD but fronto-striato-insular maldevelopment in ASD, both underpinned by shared reduced prefrontal control (see Chapter 4; (Carlisi et al., 2016b)).

Both disorders also share deficits in so-called 'hot' executive functions (EF) involving incentives and motivation (Zelazo and Müller, 2007) including reward-based decision-making measured by choice impulsivity tasks of gambling and temporal discounting (TD) (Hill, 2004, Sanders et al., 2008, Abramovitch et al., 2013, Chen et al., 2016). TD requires choosing between receiving small immediate rewards and larger later rewards, assessing the extent to which a reward is subjectively discounted when delayed in time (Rubia et al., 2009a). The ability to inhibit immediate reward choices and wait for larger rewards depends on well-developed frontal lobe-mediated motivation control and temporal foresight and is key for adult mature decision-making. A delay discounting function is typically hyperbolic, with steeper rates reflecting more impulsive choice behaviour (Richards et al., 1999). TD matures with age (Christakou et

al., 2011, Steinbeis et al., 2016) and varies among individuals (Odum, 2011), with steeper TD observed in younger people and individuals with ADHD and related impulsive disorders (Rubia et al., 2009a, Noreika et al., 2013). Functional magnetic resonance imaging (fMRI) studies of TD in healthy adults and children implicate ventromedial-fronto-limbic regions of reward-based decision-making and dorsolateral and inferior-fronto-insula-striato-parietal regions of temporal foresight (Christakou et al., 2011, Chantiluke et al., 2014b, Wesley and Bickel, 2014).

People with ASD have been shown to have deficits in reward-motivated and forward-thinking behaviour including reward processing and reversal learning (Scott-Van Zeeland et al., 2010b, Chantiluke et al., 2015a), incentive processing (Dichter et al., 2012d), planning (Ozonoff and Jensen, 1999, Geurts et al., 2004, Hill, 2004) and TD (Chantiluke et al., 2014b). However, there have also been negative findings (Antrop et al., 2006, Demurie et al., 2013). ASD is characterized by abnormalities in fronto-temporo-limbic structures which mediate socio-emotional processes (Via et al., 2011, Philip et al., 2012) (and see Chapter 4; (Carlisi et al., 2016b)), and in ventromedial/fronto-limbic brain regions involved in TD (Christakou et al., 2011, Peters and Büchel, 2011) during reward-related tasks, particularly those involving monetary reward (Schmitz et al., 2008, Dichter et al., 2012d, Kohls et al., 2013), as well as planning (Just et al., 2007). However, only one fMRI study has been published investigating the neural correlates of TD in ASD adolescents which found a weaker relationship between task-performance and bilateral superior temporal and right insular activation relative to controls (Chantiluke et al., 2014b).

Patients with OCD show deficits during planning (van den Heuvel et al., 2011, Shin et al., 2014) and reward-based tasks including goal-directed learning (Gillan and Robbins, 2014, Voon et al., 2015), reward-based decision-making, gambling (Grassi et al., 2015, Figee et al., 2016) and incentive processing (Figee et al., 2011). Despite

evidence that heightened impulsivity is a cognitive phenotype associated with OCD (Benatti et al., 2014), only one (Sohn et al., 2014) out of 3 studies of TD in OCD (Vloet et al., 2010, Pinto et al., 2014, Sohn et al., 2014) found performance deficits in patients.

Neuroimaging studies show that OCD is characterized by structural and functional abnormalities in medial and orbitofronto-striato-thalamo-cortical networks mediating EF (Menzies et al., 2008, Radua et al., 2010, Norman et al., 2016) (and see Chapter 4; (Carlisi et al., 2016b)). No fMRI studies, however, have investigated the neural correlates of TD in OCD. Studies using other reward-based decision-making tasks in OCD have found hyperactivity in ventral-affective regions including ventromedial prefrontal, orbitofrontal and rostral anterior cingulate cortex (rACC) projecting to ventral striatum and mediodorsal thalamus, and hypoactivity in dorsal-cognitive cortico-striato-thalamic regions including dorsolateral prefrontal (DLPFC), temporal and parietal association cortex projecting to the dorsal striatum and caudate in patients relative to controls (Menzies et al., 2008, Brem et al., 2012). Hypoactivation in DLPFC and caudate has furthermore been shown in OCD patients relative to controls during planning (van den Heuvel et al., 2005b, van den Heuvel et al., 2011).

This evidence suggests that ASD and OCD have abnormalities during planning and 'hot' EF tasks including reward-based decision-making, and that this may be underpinned by ventromedial and dorsolateral prefronto-striato-limbic abnormalities. However, it is unclear whether reward-based decision-making problems in both disorders are underpinned by shared trans-diagnostic mechanisms or by disorder-specific underlying abnormalities.

We hypothesized that ASD adolescents would be more impaired on TD relative to OCD adolescents and controls (Scott-Van Zeeland et al., 2010b, Chantiluke et al., 2014b, Chen et al., 2016) and that both clinical groups compared to healthy controls

would show underactivation in underlying ventromedial prefrontal, limbic and striatal regions mediating TD (Fineberg et al., 2009), reflecting a trans-diagnostic neurofunctional phenotype (Chantiluke et al., 2015a, Grassi et al., 2015, Chen et al., 2016). However, we hypothesised that people with OCD would show disorder-specific (ventro)medial and dorsolateral-prefrontal dysfunction (Menzies et al., 2008, Norman et al., 2016) (and see Chapter 4; (Carlisi et al., 2016b)) while people with ASD would show disorder-specific insular and temporo-parietal dysfunction compared to controls (Di Martino et al., 2009, Chantiluke et al., 2014b) (and see Chapter 4; (Carlisi et al., 2016b)).

6.2 Methods and materials

6.2.1 Participants

Sixty-nine right-handed (Oldfield, 1971) boys (20 controls, 29 boys with ASD, 20 boys with OCD), 11-17 years, IQ≥70 (Wechsler, 1999) participated. Medication–naïve ASD boys were recruited from local clinics and support-groups. ASD diagnosis was made by a consultant psychiatrist using ICD-10 research diagnostic criteria (WHO, 1992) and confirmed with the Autism Diagnostic Interview-Revised (ADI-R; (Lord et al., 1994)). The Autism Diagnostic Observation Schedule (ADOS; (Lord et al., 2000)) was also completed; all ASD boys reached cut-offs for ASD in all domains on the ADI-R (social, communication, restricted/stereotyped) and ADOS (communication, social). Parents of ASD boys completed the Social Communication Questionnaire (SCQ; (Rutter et al., 2003)) and the Strengths and Difficulties Questionnaire (SDQ; (Goodman and Scott, 1999)). ASD participants had a physical examination to exclude comorbid medical disorders and biochemical, haematological and chromosomal abnormalities associated with ASD. All but 5 ASD participants scored above clinical threshold for

ASD on the SCQ, and those who did not were included on the basis of a clinician-confirmed ASD diagnosis. Eight ASD participants scored above threshold for inattention/hyperactivity problems on the SDQ, but these patients were not excluded on the basis that inattention problems are common in ASD and clinician confirmation that ASD symptoms were the sole/primary clinical concern for these patients.

OCD boys were recruited from local and national OCD clinics. Diagnosis was made by a consultant psychiatrist/clinical psychologist using ICD-10 criteria and confirmed by the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS; (Goodman et al., 1989)). Parents of OCD patients completed the SDQ. Patients with comorbid psychiatric or neurological disorders, including ASD, were not included in the OCD sample, although OCD patients were not specifically assessed for ASD. Four boys were prescribed stable doses of antidepressants. One OCD patient scored above clinical cut-off for inattention/hyperactivity symptoms on the SDQ subscale, but this participant was not excluded on the basis that communication and inattention difficulties can be conflated with symptoms related to OCD and the fact that no OCD patients met criteria for ASD or ADHD based on clinical interview.

6.2.1.1 OCD patient medication status

Patient 1: Sertraline 75mg

Patient 2: Sertraline 100mg

Patient 3: Sertraline 200mg

Patient 4: Fluvoxamine 100mg; risperidone 0.5mg

Twenty age and handedness-matched healthy controls were recruited locally by advertisement. Controls scored below clinical threshold on the SDQ and SCQ for any disorder and did not have any psychiatric condition.

Exclusion criteria for all participants included comorbid psychiatric or medical disorders affecting brain development (e.g. epilepsy/psychosis), drug/alcohol dependency, head injury, genetic conditions associated with ASD, abnormal brain structural MRI scan and MRI contraindications. All controls also participated in previously published fMRI studies testing fluoxetine effects on TD in ADHD (Carlisi et al., 2016a) and neurofunctional maturation of TD in healthy adults and adolescents (Christakou et al., 2011);all but 4 ASD boys participated in our fMRI study comparing ASD and ADHD during TD (Chantiluke et al., 2014b). Most ASD and control participants also participated in other fMRI tasks during their visit, published elsewhere (Christakou et al., 2013a, Christakou et al., 2013b, Chantiluke et al., 2014a, Murphy et al., 2014, Chantiluke et al., 2015a, Chantiluke et al., 2015b).

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the local Research Ethics Committee (05/Q0706/275). Study details were explained to child and guardian, and written informed consent was obtained for all participants.

6.2.2 Temporal discounting fMRI paradigm

Prior to scanning, subjects practiced the12-minute TD fMRI task (Rubia et al., 2009a, Christakou et al., 2011, Chantiluke et al., 2014b) in a mock-scanner. Subjects choose by pressing a left or right button with right index or middle-finger between receiving a small amount of money immediately (£0-£100) or receiving £100 in one week, month or year (Figure 6.1). Delays (20 trials each) were randomised, but the delayed option (£100) was consistently displayed on the right side of the screen, and variable immediate choices on the left, to minimize sensorimotor mapping effects. In individually-adjusted TD paradigms (Richards et al., 1997, Christakou et al., 2011), the immediate reward is adjusted using an algorithm based on previous choices of the

participant for different delays to narrow the range of immediate values offered for each delay type, converging towards the value of the participant's subjective equivalent of the fixed delayed reward (Richards et al., 1999). This results in the typically hyperbolic delay discounting function.

Choices were displayed for 4s, followed by a blank screen of at least 8s (inter-trial-interval: 12s). The amount of immediate reward was adjusted through an algorithm based on previous choices and calculated separately for each of the three delays. This narrows the range of values, converging on an indifference point where the immediate reward is subjectively considered equivalent to the delayed amount for the given delay (Rubia et al., 2009a), ensuring comparable numbers of immediate and delayed choices for analysis.

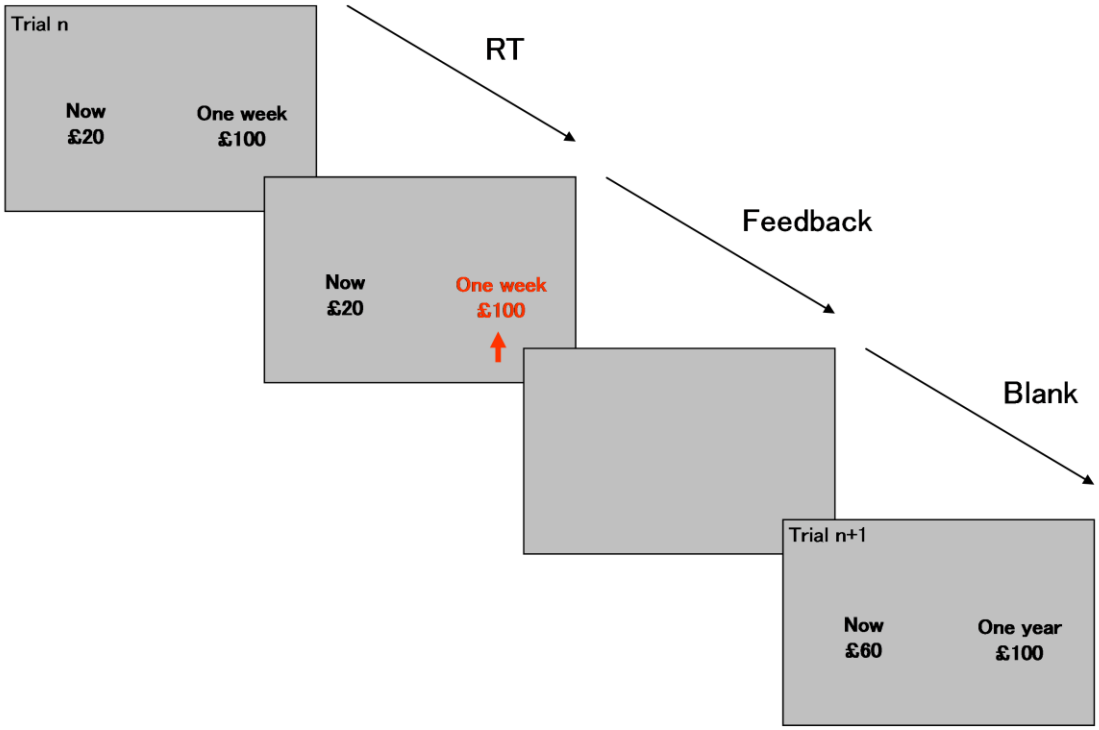


Figure 6.1 The Temporal Discounting fMRI paradigm

Subjects were asked to indicate whether they would prefer a small, variable amount of money immediately (immediate reward), or whether they would rather wait for a larger delay (up to £100) later (delayed reward). An algorithm adjusted the amount of the immediate reward offered based on the choices of the participant, so as to determine the lowest immediate reward they would tolerate before instead choosing to wait for the larger delayed reward. Three hypothetical delays were presented in random order: one week, one month and one year. Each delay choice was presented 20 times. Trials started with the presentation of the choice display, which remained available for 4s, within which the subject must choose between the immediate (always on left side) and delayed (always on right) rewards. Total trial duration was 12s.

6.2.3 Analysis of performance data

To estimate TD steepness for each subject, indifference values between the immediate amount and delayed £100 for each delay were calculated, equal to the participant's subjective value of £100 after each delay and defined as the midpoint between the lowest chosen immediate reward and the next lowest immediate reward available (i.e. the value of the immediate reward offered at which point the subject began to instead choose the delayed reward) (Christakou et al., 2011).

Reward is typically discounted as a decay function depending on amount, delay and a free impulsiveness indicator *"k"*, calculated by fitting a hyperbolic function to the indifference values for each delay. Written as $V=A/(1+kD)$, V is the subjective value of reward amount A, D is the delay and k is a constant defining the subject's rate of discounting, with larger k reflecting steeper TD (Richards et al., 1999).

However, the limitations of fMRI task adaption such as relatively few trials and only three delay points limits the goodness-of-fit of the data to a non-linear curve function. Additionally, distribution of *k*-values in this study was not normal, skewed by low-frequency high-value outliers. Thus, TD was measured using area under the curve (AUC) (Myerson et al., 2001). Smaller AUC denotes steeper discounting rates (i.e. increased choice-impulsivity). Normalized subjective values of the delayed £100 for each delay were plotted against the normalized delays, and AUC of these plots were calculated for each participant and used as the main dependent variable.

One-way between-group analysis of variance (ANOVA) was conducted with AUC as dependent measure to examine group differences.

6.2.4 fMRI image acquisition

Gradient-echo echo-planar imaging (EPI) data were acquired at King's College London on a 3T-General Electric SIGNA HDx MRI scanner (Milwaukee, WI) using the body coil for radio frequency transmission and a quadrature birdcage head coil for reception. In each of 22 non-contiguous planes parallel to the anterior-posterior commissure, 480 T2*-weighted MR images depicting BOLD (blood-oxygen level-dependent) contrasts covering the whole brain were acquired with echo time (TE)=30ms, repetition time (TR)=1.5s, flip angle=60^{o}, in-plane voxel size=3.75mm, slice thickness=5mm, slice skip=0.5mm. This EPI dataset provided almost complete brain coverage. A whole-brain high-resolution structural scan (inversion recovery gradient EPI) used for standard space normalization of individual activation maps was acquired in the inter-commissural plane with TE=30ms, TR=3s, flip angle=90^{o}, slices=43, slice thickness=3.0mm, slice skip=0.3mm, in-plane voxel-size=1.875mm, providing comprehensive coverage. Total scan was 1.5 hours during which subjects completed 2-3 additional fMRI tasks.

6.2.5 fMRI image analysis

Event-related data were acquired in randomized trial presentation and analysed using the non-parametric XBAM software package (v4.1) (www.brainmap.co.uk; (Brammer et al., 1997)). The individual and group-level analysis methods are described in detail elsewhere (Brammer et al., 1997, Bullmore et al., 1999b, Cubillo et al., 2014).

6.2.5.1 Individual analysis

Data were first processed to minimize motion-related artefacts (Bullmore et al., 1999a). A 3-D volume consisting of the average intensity at each voxel over the entire experiment was calculated and used as a template. The 3D-image volume at each time

point was realigned to this template by computing the combination of rotations (around *x*, *y* and *z* axes) and translations (*x*, *y* and *z*) that maximised the correlation between the image intensities and the volume in question and the template (rigid-body registration). Following realignment, data were smoothed using a Gaussian filter (full-width at half-maximum (FWHM) 7.2mm) to improve the signal-to-noise ratio of the images (Bullmore et al., 1999a). Following motion correction, global detrending and spin-excitation history correction, time series analysis for each subject was conducted based on previously published wavelet-based resampling methods for fMRI data (Bullmore et al., 1999b, Bullmore et al., 2001). At the individual-subject level, a standard general linear modelling approach was used to obtain estimates of the response size (beta) to each of the task conditions (delayed and immediate reward choices) against an implicit baseline. We first convolved the main experimental conditions with 2 Poisson model functions (peaking at 4 and 8s). We then calculated the weighted sum of these 2 convolutions that gave the best fit (least-squares) to the time series at each voxel. A goodness-of-fit statistic (SSQ ratio) was then computed at each voxel consisting of the ration of the sum of squares of deviations from the mean intensity value due to the model (fitted time series) divided by that of the squares due to the residuals (original time series minus model time series). The appropriate null distribution for assessing significance of any given SSQ ratio was established using a wavelet-based data re-sampling method (Bullmore et al., 2001) and applying the model-fitting process to the resampled data. This process was repeated 20 times at each voxel and the data combined over all voxels, resulting in 20 null parametric maps of SSQ ratios for each subject, which were combined to give the overall null distribution of SSQ ratio. This same permutation strategy was applied at each voxel to preserve spatial correlation structure in the data. Individual SSQ ratio maps were then transformed into standard space, first by rigid-body transformation of the fMRI data into a high-resolution

inversion recovery image of the same subject, and then by affine transformation onto a Talairach template (Talairach and Tournoux, 1988).

6.2.5.2 Group analysis

A group-level activation map was produced for each group for the experimental condition (delayed-immediate choices) by calculating the median observed SSQ ratios at each voxel in standard space across all subjects and testing them against the null distribution of median SSQ ratios computed from the identically transformed wavelet-resampled data (Brammer et al., 1997, Bullmore et al., 2001). The voxel-level threshold was first set to 0.05 to give maximum sensitivity and to avoid type-II errors. Next, a cluster-level threshold was computed for the resulting 3D voxel clusters. The necessary combination of voxel and cluster level thresholds was not assumed from theory but rather was determined by direct permutation for each dataset, giving excellent type-II error control (Bullmore et al., 1999b). Cluster mass rather than a cluster extent threshold was used to minimize discrimination against possible small, strongly responding foci of activation (Bullmore et al., 1999b).

6.2.5.3 ANCOVA of between-group effects

One-way between-group analysis of covariance (ANCOVA) with age as covariate was conducted using randomization-based testing to investigate case-control differences (Bullmore et al., 1999b, Bullmore et al., 2001). For these comparisons, statistical thresholds of 0.05 (voxel-level)/0.015 (cluster-level) were selected to obtain <1 false-positive 3D cluster per map. Standardized blood-oxygenation level-dependent (BOLD) responses were extracted from significant clusters for each participant and plotted to determine effect direction. *Post-hoc* significance was determined among pairwise comparisons using a one-way ANOVA.

6.2.5.4 Influence of behaviour, symptoms and medication

To examine whether clusters showing significant group effects were related to TD performance or symptoms, BOLD response from these clusters was extracted for each participant and Spearman correlations (two-tailed) were performed with AUC and symptom subscales within each group. FMRI analyses were also repeated including AUC as covariate.

Lastly, analyses were repeated excluding the 4 OCD participants prescribed medication.

6.3 Results

6.3.1 Participant characteristics

There were no significant group-differences in age and IQ (Table 6.1). Multivariate ANOVAs showed group-differences on SDQ scores; *Post-hoc* tests revealed that on total scores, patients scored higher than controls, with ASD being more impaired than OCD patients (all $p<0.001$). On the emotion subscale, both patient groups were more impaired than controls ($p<0.001$) but did not differ from each other. On all other SDQ subscales, ASD patients were significantly more impaired than controls and OCD patients (all $p<0.005$), who did not differ on any measure, with the exception of the conduct subscale where ASD patients differed from controls only ($p<0.001$).

Table 6.1 Participant characteristics for healthy control boys and patients with OCD or ASD

Variables	HC (N=20) Mean (SD)	ASD (N=29) Mean (SD)	OCD (N=20) Mean (SD)	*F* test (DF)	*p* value
Age (years)	15.29 (1.8)	14.72 (1.8)	15.74 (1.4)	2.22 (2,66)	0.12
IQ	118.90 (11.9)	113.17 (13.1)	117.70 (13.4)	1.38 (2,66)	0.26
SCQ total score	2.32 (2.3)	18.66 (8.1)	-	76.98 (1,47)	<0.001
SDQ total score	5.58 (4.2)	19.66 (6.8)	12.45 (5.6)	35.56 (2,66)	< 0.001
SDQ emotional distress subscale	0.93 (1.8)	4.38 (2.9)	4.35 (2.6)	13.12 (2,66)	< 0.001
SDQ conduct subscale	0.86 (1.1)	2.69 (2.2)	1.85 (1.5)	6.55 (2,66)	0.003
SDQ peer relations subscale	1.53 (1.7)	6.59 (2.3)	3.30 (3.0)	28.72 (2,66)	< 0.001
SDQ hyperactive impulsive/inattentive subscale	2.72 (2.4)	5.93 (2.6)	2.95 (2.7)	12.52 (2,66)	< 0.001
SDQ prosocial behaviour subscale	8.38 (2.4)	4.41 (2.4)	7.65 (2.6)	18.61 (2,66)	< 0.001
ADOS communication score	-	3.62 (1.2)	-	-	-
ADOS social interaction score	-	9.03 (2.3)	-	-	-
ADOS communication+social	-	12.66 (3.1)	-	-	-
ADOS stereotypy score	-	1.52 (1.5)	-	-	-
ADI communication score	-	16.59 (4.7)	-	-	-
ADI social interaction score	-	19.97 (5.3)	-	-	-
ADI repetitive behaviour score	-	6.45 (2.4)	-	-	-
CY-BOCS total score	-	-	22.33 (5.8)	-	-
CY-BOCS – obsessions	-	-	10.79 (3.6)	-	-
CY-BOCS - compulsions	-	-	12.01 (3.1)	-	-

Abbreviations: ADI, Autism diagnostic interview; ADOS, Autism diagnostic observation schedule; ASD, Autism Spectrum Disorder; CY-BOCS, Children's Yale-Brown Obsessive-Compulsive Scale; HC, healthy controls; OCD, obsessive-compulsive disorder; SCQ, social communication questionnaire; SDQ, strengths and difficulties questionnaire

6.3.2 Performance

AUC correlated inversely with *k* (as measured by the square-root transform of these values: r=-0.56, p<0.001), suggesting adequate congruency between these two metrics. AUC differed between groups [controls: 0.56±0.13; ASD: 0.45±0.24; OCD: 0.59±0.15; $F(2,66)$=4.04, p=0.02]. *Post-hoc* comparisons showed that ASD patients had significantly smaller AUC compared to controls (p<0.05) and OCD patients (p<0.01), indicating that ASD patients discounted rewards more steeply than the other groups, who did not differ from each other.

6.3.3 fMRI data

6.3.3.1 Movement

Multivariate ANOVA showed no group-differences in mean head rotation [$F(2,66)$=1.17, p=n.s.] or translation [$F(2,66)$=2.59, p=n.s.] in 3-dimensional Euclidian space.

6.3.3.2 Group maps of brain activation for delayed-immediate choices

Controls

For delayed – immediate choices, controls activated left putamen, bilateral insula and temporo-parietal regions including medial and superior temporal lobe and inferior parietal lobe (IPL), as well as posterior cingulate cortex (PCC)/precuneus and pre and post-central gyrus. For immediate – delayed choices, controls activated bilateral cerebellum and occipital lobe, IPL and right pre/post-central gyrus (Figure 6.2A).

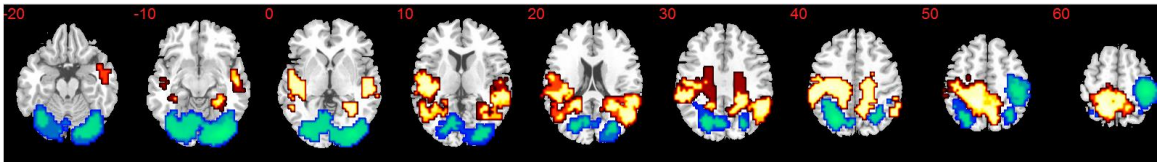
ASD patients

For delayed – immediate choices, ASD patients activated left medial temporal lobe and posterior insula, right anterior insula, medial prefrontal cortex (MPFC), PCC/precuneus, and right pre-SMA. For immediate – delayed choices, ASD patients activated bilateral cerebellum and occipital lobe, IPL, right pre/post-central gyrus, and bilateral medial and lateral fronto-striatal regions (Figure 6.2B).

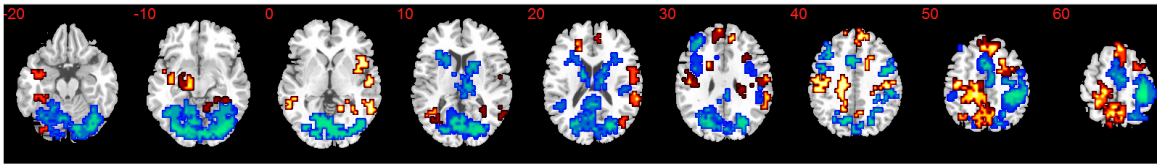
OCD patients

For delayed – immediate choices, OCD patients activated left medial temporal lobe, bilateral middle temporal gyrus, dorsal MPFC (dMPFC) and PCC/precuneus. For immediate – delayed choices, OCD patients activated bilateral cerebellum and occipital lobe, IPL and right pre/post-central gyrus (Figure 6.2C).

(A) Healthy controls



(B) ASD patients



(C) OCD patients

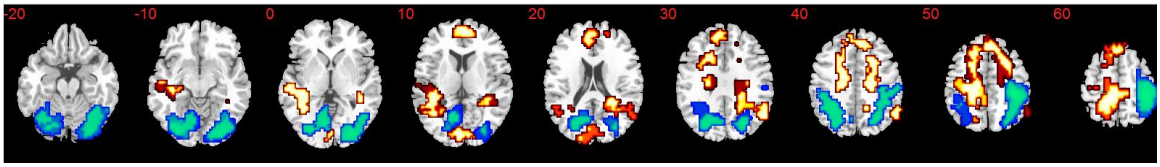


Figure 6.2 Group activation maps

Axial slices showing within-group brain activation for the contrasts of delayed-immediate reward choices (red) and immediate-delayed reward choices (blue). (A) Healthy controls, (B) ASD patients and (C) OCD patients. Talairach z-coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the brain corresponds to the right side of the image.

6.3.3.3 Group effects on brain activation for delayed minus immediate choices

One-way ANOVA showed a significant group effect for delayed-immediate choices in right ventromedial orbitofrontal cortex (vmOFC) extending into MPFC/lateral OFC/inferior frontal cortex (IFC), in lateral cerebellum extending into occipital lobe/posterior cingulate (PCC)/precuneus, in rACC/vmPFC extending into left caudate, in left superior/middle temporal lobe (STL/MTL)/inferior parietal lobe (IPL) and in right MTL/STL extending into posterior insula/postcentral gyrus/IPL (Figure 6.3A; Table 6.2). ANCOVA including AUC as covariate showed that effects in rACC/vmPFC and PCC/precuneus were related to task performance.

Post-hoc analyses based on extracted SSQs showed that abnormalities in vmOFC/MPFC/IFC were shared between OCD and ASD patients, who both had increased activation to immediate-delayed choices relative to controls (both $p<0.001$), who had more activation in this cluster to delayed choices. In lateral cerebellum/occipital lobe/PCC/precuneus, ASD and OCD patients had reduced activation to delayed-immediate choices compared to controls (both $p<0.001$). In rACC/vmPFC/caudate, both patient groups had decreased activation to immediate-delayed choices relative to controls (ASD: $p<0.001$; OCD: $p<0.05$), who had enhanced activation to immediate-delayed choices, but this effect was more pronounced in ASD versus OCD patients at trend-level ($p<0.1$). Findings in right MTL/STL/insula/postcentral gyrus/IPL (all $p<0.005$) and left STL/MTL/IPL were due to shared abnormalities in ASD ($p<0.001$) and OCD ($p<0.005$) patients, who had less activation to immediate-delayed choices relative to controls who activated this region for immediate versus delayed choices (Figure 6.3B). When the four OCD patients prescribed medication were excluded from analyses, main findings remained, suggesting medication did not influence task-related activation.

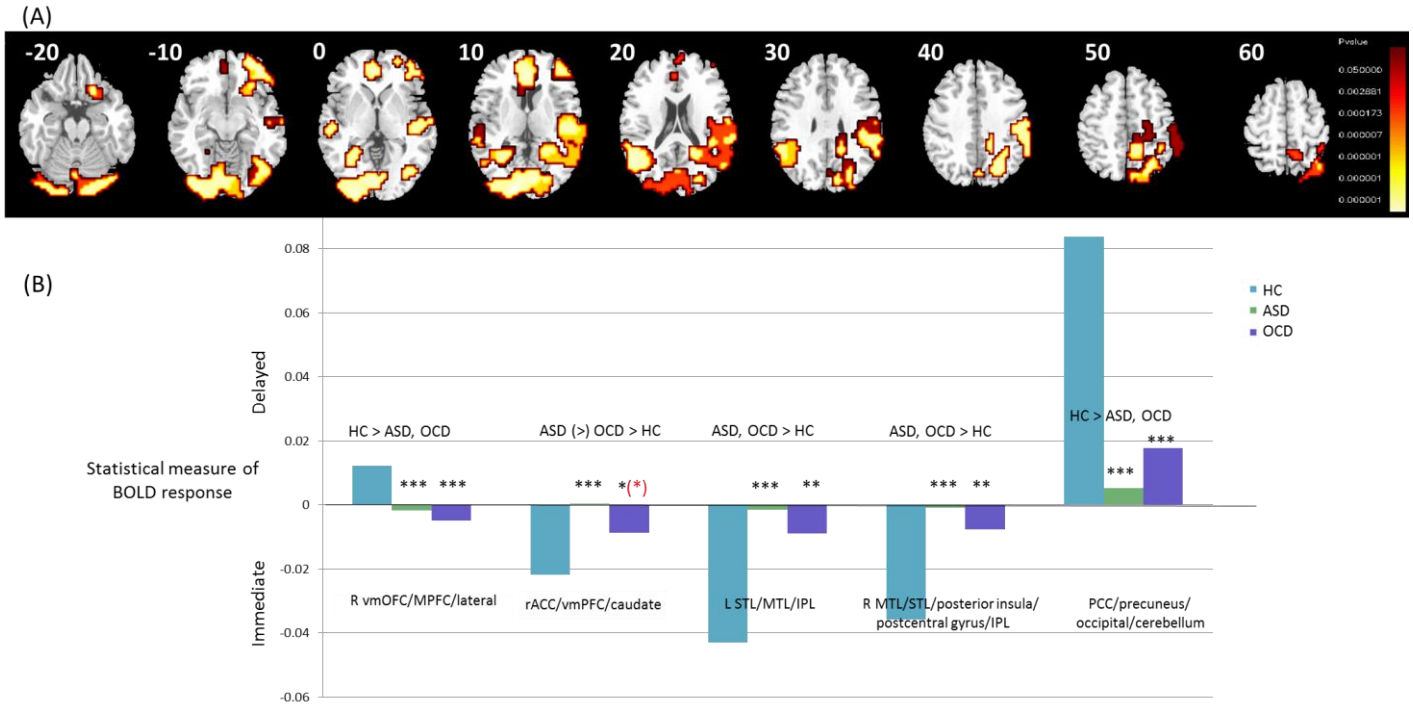


Figure 6.3 Between-group activation differences for delayed minus immediate choices

(A) Axial slices showing split-plot analysis of variance (ANOVA) effects of group on brain activation to delayed – immediate choices. Talairach *Z* coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the image corresponds to the right side of the brain.
(B) Extracted statistical measures of BOLD response are shown for each of the three groups for each of the brain regions that showed a significant group effect. **Black** asterisks indicate a significant difference between controls and patient group. **Red** asterisk indicates a difference between the two patient groups. (*)= significant at a trend level; *=significant at the $p<.05$ level; **=significant at the $p\leq.005$ level; ***=significant at the $p\leq.001$ level.
Abbreviations: ASD, autism spectrum disorder; BOLD, blood oxygen level dependent; HC, healthy controls; IFC, inferior frontal cortex; IPL, inferior parietal lobe; LOFC, lateral orbitofrontal cortex; L, left; MPFC, medial prefrontal cortex; MTL, middle temporal lobe; OCD, obsessive-compulsive disorder; PCC, posterior cingulate cortex; R, right; rACC, rostral anterior cingulate cortex; STL, superior temporal lobe; vmOFC, ventromedial orbitofrontal cortex. See Appendix B for graphs including standard error bars.

Table 6.2 Between-group activation differences for delayed minus immediate choice

Brain regions of activation difference	Brodmann Area (BA)	Peak Talairach coordinates (x,y,z)	Voxels	Cluster *p* value
(A) HC > OCD, ASD				
R vmOFC/MPFC/lateral OFC/IFC	47/11/25/10/46	40,56,-13	189	0.009
PCC/precuneus/occipital lobe/ lateral cerebellum	31/7/19/18/17	-14,-89,4	1060	0.0003
(B) OCD, ASD > HC				
rACC/vmPFC/left caudate	10/32/24	0,41,4	137	0.01
L STL/MTL/IPL	22/39/40/7/19	-51,-56,9	273	0.005
R MTL/STL/posterior insula/ postcentral gyrus/IPL	22/39/19/5/3/1/2/4/ 40/7	61,-22,9	654	0.001

Abbreviations: ASD, autism spectrum disorder; HC, healthy controls; IFC, inferior frontal cortex; IPL, inferior parietal lobe; L, left; MTL, middle temporal lobe; OCD, obsessive-compulsive disorder; OFC, orbitofrontal cortex; R, right; STL, superior temporal lobe; rACC, rostral anterior cingulate cortex; vmOFC, ventromedial orbitofrontal cortex; vmPFC, ventromedial prefrontal cortex

6.3.3.4 Correlations between differentially activated brain regions and performance

Correlations between areas that differed between groups and AUC showed that greater activation to delayed-immediate choices in lateral cerebellum/occipital lobe/PCC/precuneus was correlated with less-steep TD in the ASD (r=0.66, p<0.001) and OCD groups (r=0.45, p<0.05). Greater activation to immediate-delayed choices in left STL/IPL correlated with less-steep TD performance in the ASD group (r=-0.41, p<0.05). In right MTL/STL/insula/postcentral gyrus/IPL, it correlated with better TD performance in both ASD (r=-0.39, p<0.05) and OCD (r=-0.59, p<0.005)[1].

6.3.3.5 Correlations between differentially activated brain regions and symptoms in patients

In the ASD group, greater activation to delayed versus immediate choices in right vmOFC/MPFC/lateral OFC/IFC correlated at trend-level with lower symptom severity on the repetitive behaviour subscale of the ADI-R (r=-0.34, p=0.07). In bilateral STL/insula, lower repetitive behaviour symptom severity was related to increased activation to immediate versus delayed choices in the ASD group (left: r=0.47, p<0.01; right: r=0.42, p<0.05). In the OCD group, increased activation to delayed-immediate choices in cerebellum/occipital lobe/PCC/precuneus correlated with lower symptom severity on the CY-BOCS compulsions subscale (r=-0.58, p<0.01). There were no correlations between activation and other subscales from the CY-BOCS in OCD or ADOS/ADI-R in ASD.

6.4 Discussion

Results of this first comparison between patients with ASD and OCD on a 'hot' EF measure of reward-based decision-making showed disorder-specific impaired TD in

[1] Formal comparisons of correlations between groups using Fisher's r-to-z transformation are reported in Appendix C

ASD relative to OCD boys and controls. Despite this performance impairment in ASD boys, the findings showed predominantly shared neurofunctional deficits in key TD areas relative to healthy controls including vmOFC/MPFC/IFC, bilateral temporo-parietal and cerebellar regions, suggesting that the neural basis of TD is a trans-diagnostic feature of both disorders. In only one region, ACC/vmPFC extending into caudate, ASD boys had, at trend-level, more severe underactivation relative to OCD and controls for immediate versus delayed choices.

The finding of disorder-specific performance impairments in ASD relative to OCD boys extends previous findings of impairments in ASD during TD (Chantiluke et al., 2014b), although there have been negative findings (Demurie et al., 2012). The absence of performance differences between OCD patients and controls is in line with previous studies (Vloet et al., 2010, Pinto et al., 2014), although there have been positive findings (Sohn et al., 2014). This finding of a TD deficit exclusive to ASD lends support to the distinction between impulsive and compulsive behaviours (Robbins et al., 2012), suggesting that while both disorders exhibit deficits in top-down cognitive control and related circuitry (Dalley et al., 2011), ASD individuals exhibit more impulsive decision-making during TD, as evidenced by disorder-specific impairments, while OCD patients are more habitually compulsive, supported by intact choice behaviour.

Both patient groups had reduced activation relative to controls to delayed versus immediate choices in ventromedial and ventrolateral OFC/IFC. Ventromedial and ventrolateral fronto-limbic regions are key temporal foresight areas (Christakou et al., 2011, Peters and Büchel, 2011). vmOFC has been associated with context-sensitive evaluation, e.g. adaptive incorporation of information including value, frequency, cost and impact which are integrated to calculate discounted reward value. Moreover, right

IFC is a key TD region important for working memory, attention to time and integration of external information with internal value representations, supporting goal-directed EF and mediation of temporal foresight (Wittmann et al., 2007, Rubia et al., 2009a, Carlisi et al., 2016a). It is also a hub region for cognitive control, important for the inhibition of immediate reward choices as well as future reward representation and inter-temporal bridging (Wiener et al., 2010, Radua et al., 2014b). vmOFC activation has previously been shown to be abnormal during reward-related decision-making in both OCD (Bari and Robbins, 2013, Stern and Taylor, 2014) and ASD (Dichter et al., 2012d, Kohls et al., 2013).

Compared to controls, who had enhanced activation in PCC/precuneus/occipital lobe/cerebellum to delayed-immediate choices, both patient groups showed reduced activation in these regions. These areas are important parts of fronto-limbic-parieto-cerebellar networks involved in motivation, reward evaluation and reward response (Vogt et al., 1992, McCoy et al., 2003) and are key for visual-spatial attention (Mesulam, 1999). The cerebellum is typically activated during delayed choices in healthy populations and has been associated with future outcome expectancy and temporal bridging (Smith et al., 2003, Wittmann et al., 2007, Rubia et al., 2009a, Wittmann et al., 2010, Christakou et al., 2011, Peters and Büchel, 2011, Noreika et al., 2013). We previously found similar effects of reduced activation in this region in ADHD patients relative to controls during the same task, suggesting that cerebellar underactivation maybe a trans-diagnostic feature of disorders that are challenged in TD (Rubia et al., 2009a). Moreover, enhanced activation in this region correlated in both patient groups with better performance and in the OCD group with lower symptom severity, suggesting a link between the integrity of this activation for task performance and an association between OCD symptom severity and poorer cerebellar activation. This collectively provides first evidence for shared functional abnormalities in

ventromedial and ventrolateral fronto-parieto-striato-cerebellar regions between ASD and OCD.

Conversely, relative to controls, who had more activation to immediate-delayed choices in rACC/vmPFC reaching into caudate, both patient groups had reduced activation to immediate choices in these regions. However, these abnormalities were at trend-level more pronounced in ASD relative to OCD. rACC is a key region mediating decision conflict (Pochon et al., 2008) and typically is increased in activation with decision difficulty during intertemporal choice (Pine et al., 2009). In the context of TD, valuation signals in rACC correlate with changes in impulsivity during different experimental conditions (Peters and Büchel, 2010), suggesting a role for the ACC/MPFC in context-dependent changes in decision-making (Peters and Büchel, 2011) as well as time accumulation (Wiener et al., 2010). Our recent meta-analysis of structural and functional MRI studies also found shared reductions in this region in ASD and OCD relative to controls both in volume and in activation during cognitive control (see Chapter 4; (Carlisi et al., 2016b)). In this study, however, we found that this dysfunction was trend-wise more impaired in ASD, implying a gradual rather than dichotomic effect of more severe impairment in ASD relative to OCD.

Regarding decreased activation in both patient groups in vmPFC during immediate versus delayed choices, we showed previously that vmPFC activation to immediate choices during TD increases with age and AUC, indicating an increase in delay-tolerant behaviour linked to increased limbic-corticostriatal activation with age (Christakou et al., 2013a). In children and adults, steeper TD has been associated with a neural imbalance between reduced activation in ventromedial prefrontal and lateral frontal systems mediating evaluation of future reward and temporal foresight, and reduced top-down control over ventral-striatal and limbic systems which respond to

immediate reward (Christakou et al., 2011, Peters and Büchel, 2011, Chantiluke et al., 2014b). The finding of shared vmPFC reduction in patients relative to controls suggests similarly immature patterns of vmPFC-mediated decision-making. Moreover, tasks indexing vmPFC functioning and connectivity have shown age-dependent increases in sensitivity to future consequences (Crone and van der Molen, 2004) and behavioural control during TD (Steinbeis et al., 2016). This link is supported by fMRI findings on the Iowa Gambling Task (Bechara et al., 1994) where vmPFC activation mediated adaptive decision-making via outcome evaluation and was related to trait impulsivity (Christakou et al., 2009a) as well as age-related findings in the vmPFC during TD (Christakou et al., 2011, Steinbeis et al., 2016). Moreover, this extends models of adolescent development suggesting immature prefrontal control over hyper-responsive limbic systems (Casey et al., 2008) by showing that adolescents with OCD and ASD may exhibit immature patterns of development within reward-based decision-making circuitry.

The left caudate, which was also underactivated in both patient groups during immediate choices, is a key region involved in time discrimination (Smith et al., 2003), has been linked to reward expectation and evaluation (Hinvest et al., 2011) and has been activated during immediate choices in healthy individuals (Christakou et al., 2011). In OCD, OFC-caudate loops are proposed to drive motor impulsivity as well as compulsive behaviour (Fineberg et al., 2009, Dalley et al., 2011). Lastly, fronto-striatal dopamine has been implicated in ASD and OCD as well as in timing functions (Rubia et al., 2009a, Kriete and Noelle, 2015, Figee et al., 2016), suggesting possible shared neurochemical aetiology of the underpinnings of abnormalities in these regions. Thus, results could suggest that adolescents with ASD and OCD both have problems with context-dependent decision-making but that this is more problematic for people with ASD, potentially relating to the findings of disorder-specific behavioural deficits in the

ASD group. However, the fact that task performance did not correlate with extracted brain activation in this region in ASD limits interpretation, although this may be related to lower power to interpret behavioural relative to fMRI findings.

Posterior insula activation to immediate-delayed choices was also enhanced in controls but reduced in both patient groups relative to controls. This region is involved in reward-presentation and receipt (Elliott et al., 2000) as well as interoception and outcome predictability (Singer et al., 2009), is important for saliency detection and interacts with other regions to regulate reactivity to salient stimuli (Menon and Uddin, 2010). Moreover, the insula has been associated with decision-making in the context of prior risk (Xue et al., 2010) and is important for the integration of temporal-affective information (Elliott et al., 2000) and temporal encoding (Wittmann et al., 2010). The insula has been shown to be activated during risky responses, suggesting involvement in somatic state evaluation in the context of risk (Paulus et al., 2003). While previous studies have found specifically anterior insula activation during TD in children (Rubia et al., 2009a) and adults (Tanaka et al., 2004, Bickel et al., 2009, Hinvest et al., 2011), the present results highlight a differential role for the posterior insula in reward presentation and internal state evaluation (Elliott et al., 2000) during immediate-delayed choices and suggest that ASD and OCD share neurofunctional abnormalities in posterior insula relative to controls during presentation of rewards and impulsive choices.

Findings of reduced activation to immediate-delayed choices in STL/IPL in ASD relative to controls are in line with evidence of weaker brain-behaviour correlations in this region in ASD relative to controls during TD (Chantiluke et al., 2014b) and extend these findings to OCD. These regions are important for temporal coding and reward selection (Cardinal, 2006, Christakou et al., 2011), suggesting

deficits with planning, consistent with behavioural deficits in this domain in ASD (Hill, 2004) and OCD (Shin et al., 2014). IPL is involved in inter-temporal bridging and is specifically sensitive to delay (Rubia et al., 1998) and attention-allocation to time (Ortuno et al., 2002, Coull, 2004, Rubia, 2006), as well as duration encoding (Wittmann, 2009) and quantity representation, which may contribute to inter-temporal choices regarding the IPL's role in comparing time and value (Sandrini et al., 2004). Correlations between enhanced activation to immediate choices in the patient groups and better TD performance suggest that in both groups, this upregulation is related to a shift in performance towards that of controls, providing possible mechanistic implications of this region in the context of TD behaviour. Moreover, increased activation bilaterally in this region in the ASD group correlated with lower levels of repetitive behaviours, linking performance improvement and symptom reduction to brain activation in these individuals, further highlighting the possible mechanistic underpinnings of this region in the context of repetitive behaviours and decision-making.

Clinically, the fact that these disorders exhibit shared neural underpinnings during TD has implications for identification of trans-diagnostic mechanisms which may drive similar behaviours in each disorder. While symptoms such as compulsions in OCD can sometimes appear similar to repetitive behaviours in ASD at an observational level, less is known about the mechanistic underpinnings of these behaviours and related cognitive functions and whether they are shared or disorder-specific. Thus, this first evidence of shared neural abnormalities underlying TD in these two disorders sheds light on trans-diagnostic phenotypes that could aid in future treatment targets and work toward providing a biological explanation of commonalities and differences in clinical behaviour. This has similarly been shown in the case of inhibitory control and brain structure/function differences/similarities in a recent meta-analysis comparing

ASD and OCD (see Chapter 4; (Carlisi et al., 2016b)), and this study extends this understanding to temporal foresight and decision-making.

This study's strengths include the thoroughness with which ASD individuals were assessed for the presence of ASD-related symptomatology and the exclusion of patients with psychiatric comorbidities. However, sub-threshold symptoms may have been present in the patient samples. Thus, it is possible that OCD-related symptoms were present in the ASD sample and could account for some of the neurobiological overlap in results. Additionally, four OCD patients were prescribed antidepressant medication. While there is evidence for effects of serotonin on brain function (Murphy et al., 2008, Murphy, 2010), results remained when analyses were repeated excluding these patients.

6.5 Conclusions

This is the first study to directly compare neural function between these disorders and provides novel evidence to suggest that ASD and OCD share trans-diagnostic neurofunctional abnormalities during TD in ventromedial and ventrolateral fronto-striatal and fronto-temporo-parieto-cerebellar regions important for temporal foresight and reward-related decision-making. This may drive shared problems with reward-related behaviours and delaying repetitive actions.

CHAPTER 7 - SHARED AND DISORDER-SPECIFIC NEUROCOMPUTATIONAL MECHANISMS OF DECISION-MAKING IN AUTISM SPECTRUM DISORDER AND OBSESSIVE-COMPULSIVE DISORDER

This chapter is presented as the final author-submitted manuscript version of the journal article currently under peer-review. The submitted accompanying supplementary information has been re-incorporated as part of Chapter 7 of this thesis.

7.1 Introduction

Autism Spectrum Disorder (ASD) is characterised by social and communication difficulties and restricted, repetitive behaviours (American Psychiatric Association, 2013) and affects 0.6-2.0% of the population, with a higher prevalence in males (Blumberg et al., 2013). Obsessive-Compulsive Disorder (OCD) is identified by recurrent and intrusive distressing thoughts (obsessions) and repetitive rituals (compulsions) (American Psychiatric Association, 2013) and has a prevalence of 1-3%, with a slightly higher incidence in males in paediatric samples (Ruscio et al., 2010). These highly heterogeneous and frequently comorbid disorders can sometimes be clinically difficult to separate, as symptoms such as repetitive behaviours in ASD can often resemble OCD-related compulsions (Russell et al., 2005). Such overlap has been attributed to shared genetic risk and biological mechanisms as well as diagnostic mislabelling (Russell et al., 2016), highlighting a need to understand the distinct and overlapping underlying neurobiological mechanisms of both disorders.

Executive functions (EF) are higher-order cognitive functions important for goal-directed behaviour and can be conceptualised dichotomously as “cool” EF, referring to non-emotional functions including inhibition and working memory, and “hot” EF, referring to functions with reward-based motivation including gambling and reward learning (Zelazo and Müller, 2007). Cool EF has been widely investigated in

ASD and OCD (for reviews, see (Zelazo and Müller, 2007, van Velzen et al., 2014, Norman et al., 2016) and Chapter 4; (Carlisi et al., 2016b)). However, relatively less is known about the mechanisms underlying reward-related hot EF processes in these disorders, as evidence to date has been inconsistent.

Impaired decision-making has been implicated in both ASD and OCD (Cavedini et al., 2006, Luke et al., 2012). The Iowa Gambling Task (IGT) (Bechara et al., 1994) has been widely used in healthy populations to measure reward-based decision-making and temporal foresight impairments under conditions of ambiguity, as it requires reinforcement learning to distinguish between choices that yield large immediate gains but even larger losses (risky options) leading to long-term financial losses and decks that give small gains but even smaller losses, leading to long-term financial gains at the end of the game (safe options).

There have been only five studies in ASD using the IGT (Johnson et al., 2006, Yechiam et al., 2010, South et al., 2014, Mussey et al., 2015, Zhang et al., 2015b), showing mixed results. A relatively consistent finding in both children/adolescents (Johnson et al., 2006, Yechiam et al., 2010) and adults (Mussey et al., 2015) is that ASD individuals shift more frequently between choices, possibly due to difficulties with implicit learning (Johnson et al., 2006) or exploration-focused learning strategies (Yechiam et al., 2010). Another study in adults with ASD found that the ASD group had worse performance, preferring disadvantageous decks (Zhang et al., 2015b). However, one study (South et al., 2014) in children/adolescents found superior performance in ASD adolescents relative to controls, explained by a "loss-avoidance" style of decision-making in the ASD group in contrast to a "reward-seeking" style often observed among typically developing adolescents (Smith et al., 2012).

There have been relatively more studies using the IGT in adults with OCD (e.g. (Purcell et al., 1998, Cavedini et al., 2002, Cavallaro et al., 2003, Olley et al., 2007, Cavedini et al., 2010, Starcke et al., 2010, Rocha et al., 2011, Grassi et al., 2015, Kim et al., 2015a)). The majority show impaired decision-making in patients relative to controls, with patients preferring large immediate rewards and not learning from losses, although there have also been negative findings (Nielen et al., 2002, Lawrence et al., 2006, Krishna et al., 2011). Only one study was conducted in children with OCD using the IGT which found that patients performed worse relative to controls and that this was related to symptom severity during the most severe period of illness (Kodaira et al., 2012).

The IGT taps a range of cognitive processes including reward-related decision-making, reward sensitivity, loss aversion, temporal foresight, inhibitory control (to inhibit the contextual 'thrill' of immediate gains), and exploratory behaviour. Thus, to clarify IGT performance impairments (or lack thereof) in both clinical groups, it is important to investigate these cognitive and motivational factors on a more nuanced level to better characterise task-performance, and computational modelling is a useful tool for this (Huys et al., 2016).

Similar performance deficits could also be mediated by differing underlying neurofunctional networks. No functional magnetic resonance imaging (fMRI) studies, however, have yet investigated the neural correlates of decision-making under ambiguity in ASD or OCD using the IGT. In healthy individuals, the IGT activates dorsolateral and ventromedial prefrontal, insular, posterior cingulate, orbitofrontal and ventral striatal regions during the various stages of the decision-making process (Li et al., 2010). In light of a dearth of evidence in ASD and OCD specifically on the IGT, evidence can be compiled from studies examining related reward-based decision-

making processes; during tasks of temporal discounting (Chantiluke et al., 2014b) and reversal learning (Chantiluke et al., 2015a), adolescents with ASD have shown abnormalities in related fronto-temporo-limbic systems mediating executive processes (see Chapter 4; (Carlisi et al., 2016b)) and ventromedial/fronto-limbic regions important for reward-related functions, especially those involving monetary gain/loss (Kohls et al., 2013). OCD has traditionally been conceptualized as a disorder of abnormalities in ventral affective systems including (orbito)fronto-striato-thalamo-cortical networks as well as in lateral orbitofrontal-striatal systems important for cognitive/inhibitory control (Zelazo and Müller, 2007, Menzies et al., 2008) (and see Chapter 4; (Carlisi et al., 2016b)). fMRI studies involving reward-related decision-making support evidence for abnormalities in both motivation control as well as cognitive control regions by showing that OCD patients relative to controls have hyperactivity in ventromedial prefrontal, orbitofrontal and anterior cingulate cortex (ACC) regions projecting to ventral striatum and medio-dorsal thalamus, and underactivation in cortico-striato-thalamic regions including dorsolateral prefrontal cortex (DLPFC), temporal and parietal cortices and BG (Menzies et al., 2008, Brem et al., 2012).

The relative lack of consistent findings in ASD and OCD on the IGT highlights a need for a better understanding of neurocognitive phenotypes of reward-based decision-making in these disorders. Recent efforts such as the Research Domain Criteria (RDoC (Insel et al., 2010)) stress the importance of investigating trans-diagnostic phenotypes which may be underpinned by shared and/or disorder-specific neurofunctional mechanisms. Thus, we compared adolescents with ASD to those with OCD and typically developing controls to investigate shared and disorder-specific brain function abnormalities during the IGT and compared reinforcement-learning models to examine fine-grained differences in behavioural factors that might underlie overall decision-making. We hypothesized that both patient groups would be impaired on some

aspect of task performance (Grassi et al., 2015, Zhang et al., 2015b), and more specifically that ASD individuals would show lower choice-consistency (Johnson et al., 2006, Yechiam et al., 2010). We tested whether differences were due to more nuanced shared or disorder-specific differences in decision-making styles. Based on evidence from IGT studies in healthy individuals showing that reward-based decision-making may be driven by dorsolateral and ventromedial/orbitofronto-striato-limbic function (Li et al., 2010, Christakou et al., 2013a), we hypothesised that both groups would show abnormalities in these networks (Christakou et al., 2011, Brem et al., 2012). Furthermore, based on prior evidence of neurofunctional reward-related deficits in the two disorders, we hypothesised that both disorders would show abnormal reward processing in ventromedial-fronto-temporo-limbic (Kohls et al., 2013) regions important for reward-based decision-making and temporal foresight required by the task (Menzies et al., 2008). However, we also expected disorder-specific stronger deficits in OCD, in orbitofrontal regions and in ASD in ventral striatal and anterior cingulate regions based on respective deficits in these regions observed in each disorder (Menzies et al., 2008, Kohls et al., 2013).

7.2 Methods and materials

7.2.1 Participants

64 right-handed (Oldfield, 1971) boys (20 typically-developing control boys, 24 boys with ASD, 20 boys with OCD), 11-17 years-old, IQ≥70 (Wechsler, 1999) participated. Medication-naïve ASD boys were recruited from local clinics. Clinical ASD diagnosis was made by a consultant psychiatrist using ICD-10 research diagnostic criteria (WHO, 1992) and confirmed using the Autism Diagnostic Interview-Revised (ADI-R (Lord et al., 1994)). The Autism Diagnostic Observation Schedule (ADOS

(Lord et al., 1989)) was also completed. All ASD boys reached clinical thresholds in all domains on the ADI-R (social, communication, restricted/stereotyped) and ADOS (communication, social). Parents of ASD boys also completed the Social Communication Questionnaire (SCQ (Rutter et al., 2003)) and the Strengths and Difficulties Questionnaire (SDQ (Goodman and Scott, 1999)). ASD participants had a physical examination to exclude comorbid medical disorders and any abnormalities associated with ASD. Individuals with comorbid psychiatric conditions, including OCD and ADHD, were not included.

All but 3 ASD participants scored above clinical threshold for ASD on the SCQ, but these patients were included on the basis of clinician-confirmed ASD diagnosis. Six ASD participants also scored above threshold for inattention/hyperactivity symptoms on the SDQ but were not excluded on the basis that attention problems are common in ASD and clinician confirmation that ASD symptoms were the sole/primary clinical concern for these patients.

OCD boys were recruited from the Maudsley Hospital National & Specialist OCD clinic. Diagnosis was made by a consultant clinician using ICD-10 criteria and confirmed with the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS (Goodman et al., 1989)) and ancillary symptom checklist. Parents of OCD boys also completed the SDQ. OCD patients with comorbid psychiatric or neurological conditions, including ASD and ADHD, were excluded. Four boys were prescribed stable doses of antidepressants.

One OCD patient scored above clinical cut-off for inattention/hyperactivity symptoms on the SDQ but was not excluded on the basis that communication and attention difficulties can be misconstrued for OCD-related symptoms and the fact that no OCD patients met criteria for ASD or ADHD based on clinical interview.

7.2.1.1 OCD patient medication status

Patient 1: Sertraline 75mg

Patient 2: Sertraline 100mg

Patient 3: Sertraline 200mg

Patient 4: Fluvoxamine 100mg; risperidone 0.5mg

Twenty age- and handedness-matched typically-developing control boys were recruited locally by advertisement. Controls did not meet clinical threshold on the SDQ and SCQ for any disorder and did not have a current or lifetime history of any psychiatric condition.

Exclusion criteria for all subjects were comorbid psychiatric/medical disorders affecting brain development (e.g. epilepsy/psychosis), drug/alcohol dependency, history of head injury, genetic conditions associated with autism, abnormal structural MRI scans and MRI contraindications. Controls also participated in our fMRI study testing maturation of decision-making on the IGT, published previously (Christakou et al., 2013a). Most ASD and control participants also participated in additional fMRI tasks during their visit, published elsewhere (Christakou et al., 2011, Christakou et al., 2013b, Chantiluke et al., 2014a, Murphy et al., 2014, Chantiluke et al., 2015a, Chantiluke et al., 2015b, Carlisi et al., 2016a).

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the local Research Ethics Committee (05/Q0706/275). Study details were explained to participants and guardians. Written, informed assent/consent was obtained for all participants, and individuals were compensated for their time and travel expenses.

7.2.2 Iowa Gambling Task

The fMRI version of the IGT used in this study is described in detail elsewhere (Christakou et al., 2009a, Christakou et al., 2013a) and depicted in Figure 7.1. Briefly, on each of 80 trials, participants were presented with four card decks (A/B/C/D) on a screen and instructed to choose any deck by pressing the corresponding button with the right hand on an MR-compatible 5-button response box. They were instructed to win as much money as possible by the end of the task. They were only told that sometimes they would win money and sometimes they would lose money, and that some decks might be better than others. They were also told that their final amount won on the task would determine how much of a maximum £30 they would receive as compensation (in reality, all subjects received £30).

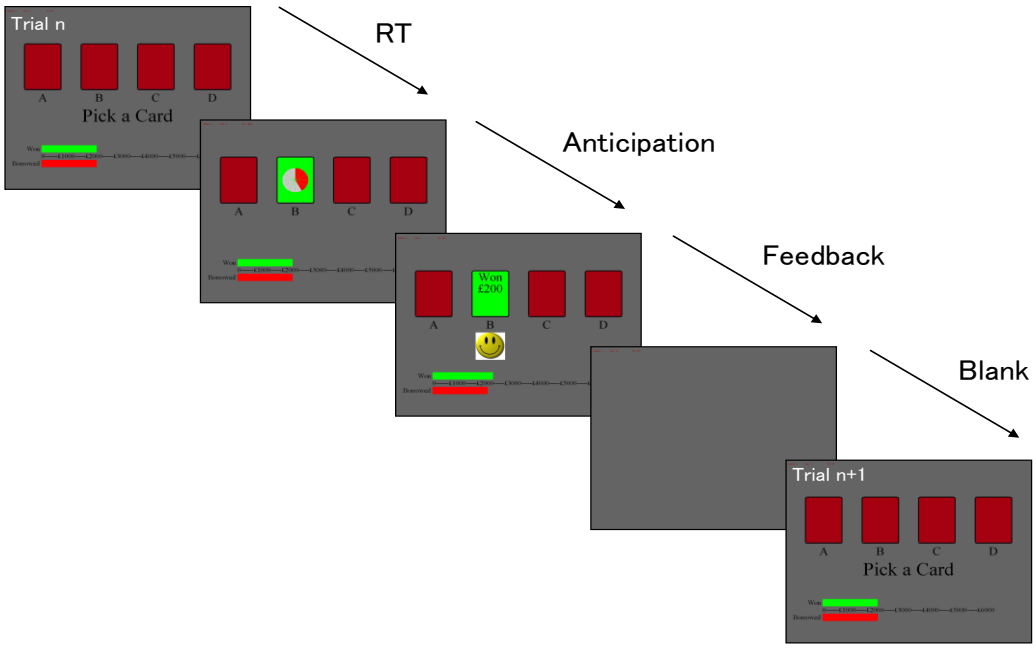


Figure 7.1 The Iowa Gambling Task fMRI adaptation

Adapted from Christakou et al., 2013. Subjects were presented with 4 decks of cards, A, B, C and D and given 3 seconds to choose any deck. After a choice was made, the chosen deck was overlaid with a 12 segment wheel, counting down for 6 seconds before the top card on the chosen deck was revealed. Winning cards were green, displaying the amount won and a happy face below the deck. Losing cards were red, displaying the amount lost and a sad face below the deck. All subjects started the task with £2000, indicated along the bottom of the screen by the red bar. Total gains were reflected by the green bar, which moved left if money was lost, but right if money was won.

Decks A and B were termed disadvantageous or "risky" decks because they returned relatively large gains (£190/£200/£210) but even larger losses (£240/£250/£260), leading to an overall net loss, whereas decks C and D were advantageous or "safe" because they returned small gains (£90/£100/£110) but even smaller losses (£40/£50/£60), resulting in a net gain. There was a 50% probability of winning or losing on each deck.

Task-performance is summarised by the ratio of advantageous choices to total choices or, the number of cards picked from decks C+D divided by the total number of cards picked (A+B+C+D). This ratio is proportional to the "net score" ((C+D)-(A+B)) frequently used when quantifying performance on the IGT (Bechara et al., 1994) without giving negative values. Ratios above 0.5 denote preference for safe relative to risky decks, while a ratio below 0.5 implies perseveration on risky choices despite accumulating losses. Responses where reaction time (RT) was less than 200ms were considered 'premature' and these trials were not included in analyses (Thorpe et al., 1996).

This IGT task adaptation differs from other fMRI versions (e.g. (Lawrence et al., 2009)) in that choice was temporally separated from its outcome, haemodynamically decoupling choice and outcome evaluation, allowing separate examination of each. Subjects were given 3 seconds to respond. Following each choice, the chosen deck was superimposed with a 12-segment wheel ticking down every 0.5s for a total 6s until outcome presentation. If no response was made, the trial progressed directly to a blank screen for 9s. Positive (win) and negative (loss) outcomes were indicated by a happy or sad face presented below the deck and the amount won or lost indicated on the card. Outcomes were presented for 3s. Trials lasted 15s, ending with a blank screen after outcome presentation, serving as an implicit baseline in the fMRI analysis. Omitted

trials were excluded from analyses. The length of each inter-trial interval (ITI) was determined by the RT, which jittered trial events so as to maintain a 15s total trial duration. As these manipulations lengthened trial and task duration compared to other behavioural variants, this version of the task included 80 trials rather than the typical 100 trials (Bechara et al., 1994, Lawrence et al., 2009). Total task time was 21mins. Before testing, participants practiced the task in a mock scanner, where 10 test trials presented equal payoffs across decks.

7.2.3 Computational modelling

The IGT requires decision-making based on the learned outcomes of previous choices. Performance on the IGT can be influenced by a range of factors including learning rates, reward and loss sensitivity, or inconsistent responding (Ahn et al., 2014). Thus, computational approaches are especially useful for understanding the processes underlying IGT performance. We used hierarchical Bayesian analysis (HBA) implemented within the hBayesDM R package (https://cran.r-project.org/web/packages/hBayesDM/index.html) for computational modelling of IGT performance (Ahn et al., 2016). For further details of the methods, rationale and advantages of HBA over other modelling methods (e.g. maximum likelihood estimation), see (Lee, 2011). HBA involves preparation of trial-by-trial task data for each participant, model fitting and comparison of three commonly used and validated models of the IGT: the *Prospect Valence Learning (PVL)-Decay Reinforcement Learning (RI)* model, the *PVL-Delta* model and the *Value-Plus-Perseverance* (*VPP*) model (Worthy et al., 2013a, Ahn et al., 2014, Steingroever et al., 2014).

7.2.3.1 The PVL-DecayRI and PVL-Delta models

In the prospect valence learning models, outcome evaluation is assessed according to the prospect utility function. The utility *u(t*) on trial *t* of each outcome *x(t)* is expressed as:

$$u(t) = \begin{matrix} x(t)^a & if\ x(t) \geq 0 \\ -\lambda|x(t)|^a & if\ x(t) < 0 \end{matrix} \qquad (1)$$

α (0< α<2) determines the shape of the utility function, and the loss-aversion parameter λ (0< λ <10) determines sensitivity to losses versus gains. Higher α implies greater sensitivity to feedback, and a value of λ<1 indicates higher sensitivity to gains than losses (whereas λ>1 indicates the opposite).

The PVL models are identical except that they use different learning rules. The parameter *A* determines how much past expectancy is discounted; in the decayRI learning rule, expectancies of all decks are discounted on each trial, and the expectancy of the chosen deck is updated by current outcome utility:

$$E_j(t+1) = A \cdot E_j(t) + \delta_j(t) \cdot u(t) \qquad (2)$$

In the delta rule, only the expectancy of the selected deck is updated while expectancies of the other decks is unchanged:

$$E_j(t+1) = E_j(t) + A \cdot \delta_j(t) \cdot (u(t) - E_j(t)) \qquad (3)$$

Thus, learning rate *A* determines how much weight is placed on past experiences vs. most recent experience of the chosen deck. A high learning rate indicates that the recent outcome has a large influence on expectancy of the chosen deck (i.e. 'forgetting' is more rapid) while a low learning rate indicates the opposite. Next, a softmax function (Luce, 1959) is used to calculate the probability of choosing deck *j*, with sensitivity (θ)

determining the degree of exploitation vs. exploration. *c* is a choice consistency (sensitivity) parameter:

$$\Pr[D(t+1)=j]=\frac{e^{\theta\cdot E_j(t+1)}}{\sum_{k=1}^{4}e^{\theta\cdot E_k(t+1)}} \qquad (4)$$

7.2.3.2 Value-Plus-Perseverance model

Evidence suggests that participants frequently use a win-stay-lose-switch (WSLS) strategy, that is, a perseverative strategy that cares only about the last choice's outcome for making a choice on the current trial during reward-based learning and decision-making (Worthy et al., 2013b). Based on a model comparison between the *PVL-DecayRI* and WSLS models showing that each model respectively was the best fit for only half of the subjects investigated, a hybrid VPP model was developed (Worthy et al., 2013b) combining the PVL-Delta and perseverance heuristic. This model assumes that individuals track expectancies *($E_j(t)$)* and perseverance strengths *($P_j(t)$)*; expectancies are computed using the learning rule of the PVL-Delta model, and three additional perseverance parameters are included:

$$P_j(t+1)=\begin{cases}k\cdot P_j(t)+\varepsilon_p & if\ x(t)\geq 0\\ k\cdot P_j(t)+\varepsilon_n & if\ x(t)<0\end{cases} \qquad (5)$$

k ($0<k<1$) determines how much perseverance strengths of all (including unselected) decks decay on each trial, and ε_p and ε_n indicate loss/gain impact, respectively, on choice behaviour. Positive values reflect a tendency to persevere on the same deck, while negative values indicate a tendency to switch decks on the next trial. Overall value, $V_j(t+1)$ is the weighted sum of $E_j(t+1)$ and $P_j(t+1)$:

$$V_j(t+1)=\omega\cdot E_j(t+1)+(1-\omega)\cdot P_j(t+1) \qquad (6)$$

ω is the reinforcement learning (RL) weight (0<ω<1); a low ω indicates the subject relies less on RL/more on perseverance. Choice probability was again computed using the softmax function, but with $V_j(t+1)$:

$$\Pr[D(t+1)=j] = \frac{e^{\theta \cdot V_j(t+1)}}{\sum_{k=1}^{4} e^{\theta \cdot V_k(t+1)}} \qquad (7)$$

7.2.3.3 Hierarchical Bayesian analysis

HBA is a more suitable approach for parameter estimation compared to e.g. Maximum Likelihood Estimation (MLE) for considering individual differences through the use of posterior distributions and Markov chain Monte Carlo (MCMC) sampling algorithms (Ahn et al., 2014). Parameter estimates obtained through traditional methods such as MLE are generally estimated at the individual level from point estimates that maximize the likelihood of data for each individual subject (Myung, 2003). However, these MLE estimates can be noisy, particularly in samples with insufficient amounts of data. To address this, group-level analysis estimating a single set of parameters for an entire group may provide more reliable estimates but consequently ignores fine-grained individual differences (Ahn et al., 2016).

Bayesian statistics rely on the use of prior distributions, estimating model parameters and updating these prior using posterior distributions on a trial-by-trial basis given the data using Bayes' rule. In HBA, hyper-parameters are derived in addition to parameters introduced at the individual level (Gelman et al., 2014a). These hyper-parameters are set with group-level means and standard deviations, where the resulting joint posterior distribution $P(\Theta, \Phi|D)$ is defined as:

$$P(\Theta, \Phi|D) = \frac{P(D|\Theta,\Phi)\mathrm{P}(\Theta,\Phi)}{P(D)} \propto P(D|\Theta)P(\Theta|\Phi)P(\Phi) \qquad (8)$$

This hierarchical structure of HBA leads to a "shrinkage effect", i.e. individual estimates are pulled closer to the group mean because they inform the group's estimate, which in turn informs the estimates of each individual (Gelman et al., 2014a). As a result, parameter estimates of each individual tend to be more stable and less noisy, as common factors among individuals are informed by group tendencies. This HBA approach is particularly beneficial when e.g. the number of trials is too small to precisely estimate individual parameters for each subject, as is likely the case in the 80-trial version of the IGT used in this study. Such advantages have been demonstrated by simulation studies showing that HBA outperforms MLE in parameter recovery (Ahn et al., 2011). Lastly, HBA provides full posterior distributions rather than point estimates, thus facilitating group comparisons in a Bayesian manner (Guitart-Masip et al., 2012). For further information on HBA and its implementation in hBayesDM, refer to (Ahn et al., 2016).

7.2.3.4 Model fitting and comparison

Posterior inference for all models was performed via Markov Chain Monte Carlo (MCMC) sampling implemented in RStan (http://mc-stan.org/interfaces/rstan). Stan (v2.1.0 (Carpenter et al., 2016)) uses a specific probabilistic sampler called Hamiltonian Monte Carlo (HMC) to sample from the posterior distribution. For details, see (Kruschke, 2014, Ahn et al., 2016) and the Stan reference manual (http://mc-stan.org/documentation/).

hBayesDM enables model fit assessment and *post-hoc* comparison via Widely Applicable Information Criterion (WAIC) (Watanabe, 2010). This index is obtained by computing the summed point-wise log-likelihood per participant, accounting for the fact that in the IGT, choices on a given trial are dependent on previous choices (Gelman et

al., 2014b). Smaller WAIC scores denote better model-fit, and overall fit is assessed by adding WAIC scores from each group for each model.

7.2.4 Statistical analysis

All analyses were conducted in JASP (v0.7.5.6; https://jasp-stats.org/) using Bayesian analysis based on posterior probabilities rather than frequentist *p*-values, which rely on the sampling intentions of the investigator. JASP pre-defined priors were used. Models were favoured if BF_{10}>10, indicating strong evidence for the tested model over the null hypothesis. In instances where BF_{10} was sufficiently large (>1000), Log(BF_{10}) is reported, where values >1 indicate strong evidence for the model. For clarity, where appropriate, we also report null-hypothesis significance test (NHST) results, including *p*-values.

ANOVAs tested for group-differences in demographic and questionnaire measures, and in task performance. Group-differences in mean parameter estimates were assessed by each parameter's highest density interval (HDI), i.e. the range of parameter values which spans 95% of the distribution in a pairwise comparison (Ahn et al., 2014). A parameter was considered to significantly differ between groups if the HDI did not overlap 0. Kendall's Tau rank correlations were conducted to test for associations between task performance, symptoms and brain activation.

7.2.5 fMRI acquisition

Gradient echo echo-planar magnetic resonance imaging data were acquired on a GE Signa 3-Tesla scanner (General Electric, Waukesha WI) at the Centre for Neuroimaging Sciences, King's College London, using a semi-automated image quality-control procedure (Simmons et al., 1999). A quadrature birdcage head coil was

used for radiofrequency transmission and reception. In each of 22 non-contiguous places, we acquired 800 T_2*-weighted images depicting blood oxygenation-level dependent (BOLD) response covering the whole brain (echo time (TE)=30ms, repetition time (TR)=1.5s, flip angle=60^o, in-plane resolution=3.75mm, slice thickness=5.0mm, slice skip=0.5mm). A whole-brain high-resolution structural image with 43 slices was also acquired (TE=40ms, TR=3s, flip angle=90^o, slice thickness, 3.0mm, slice skip=0.3 mm).

7.2.6 fMRI data analysis

fMRI data were analysed using a non-parametric permutation-based software developed at the Institute of Psychiatry, Psychology and Neuroscience (XBAM v4.1; http://brainmap.co.uk) which avoids issues such as false positives that are related to parametric statistical analyses (Eklund et al., 2016). In contrast to normal theory-based inference, this approach minimizes assumptions and uses median rather than mean-based statistics to control for outlier effects. Its most commonly used test statistic is computed by standardizing for individual differences in residual noise before performing second-level multi-subject testing using robust permutation-based methods. This allows a mixed-effects approach to analysis that has been recommended following analysis of the validity and impact of theory-based inference in fMRI (Thirion et al., 2007). Details of individual and group-level analyses are also described in (Christakou et al., 2009a).

7.2.6.1 Individual-level analysis

Data were first processed to minimize motion-related artefacts (Bullmore et al., 1999a). A 3D volume consisting of the average intensity at each voxel over the entire experiment was calculated and used as a template. The 3D image volume at each time

point was then realigned to this template by computing the combination of rotations (around the *x*, *y* and *z* axes) and translations (in *x*, *y* and *z* dimensions) that maximised the correlation between the image intensities and the volume in question and the template (rigid-body registration). Following realignment, data were then smoothed using a Gaussian filter (full-width at half-maximum (FWHM) 8.82 mm) to improve the signal-to-noise ratio of the images (Bullmore et al., 1999a). Following motion correction, global detrending and spin-excitation history correction, time series analysis for each subject was conducted based on a previously published wavelet-based resampling method for fMRI data (Bullmore et al., 1999b, Bullmore et al., 2001). At the individual subject level, a standard general linear modelling approach was used to obtain estimates of the response size (beta) to each of the task conditions (choice, anticipation and outcome phases) against an implicit baseline. We first convolved the main experimental conditions with 2 Poisson model functions (peaking at 4 and 8s). We then calculated the weighted sum of these 2 convolutions that gave the best fit (least-squares) to the time series at each voxel. A goodness-of-fit statistic (SSQ ratio) was then computed at each voxel consisting of the ration of the sum of squares of deviations from the mean intensity value due to the model (fitted time series) divided by that of the squares due to the residuals (original time series minus model time series). The appropriate null distribution for assessing significance of any given SSQ ratio was established using a wavelet-based data re-sampling method (Bullmore et al., 2001) and applying the model-fitting process to the resampled data. This process was repeated 20 times at each voxel, and the data was combined over all voxels, resulting in 20 null parametric maps of SSQ ratios for each subject. These maps were then combined to give the overall null distribution of SSQ ratio. This same permutation strategy was applied at each voxel to preserve spatial correlation structure in the data. Individual SSQ ratio maps were then transformed into standard space, first by rigid-body transformation

of the fMRI data into a high-resolution inversion recovery image of the same subject, and then by affine transformation onto a Talairach template (Talairach and Tournoux, 1988).

7.2.6.2 Group-level analysis

For the group-level analysis, less than 1 false positive-activated 3D cluster was expected at $p<0.05$ (voxel-level) and $p<0.01$ (cluster-level). A group-level activation map was produced for each group and each experimental condition (choice, anticipation and outcome) by calculating the median observed SSQ ratios at each voxel in standard space across all subjects and testing them against the null distribution of median SSQ ratios computed from the identically transformed wavelet-resampled data (Brammer et al., 1997, Bullmore et al., 2001). The voxel-level threshold was first set to 0.05, and tests were conducted to identify voxels that might be plausibly activated followed by a test at a cluster-level threshold of $p<0.01$ to remove the false-positive clusters produced by the voxel-level test (Bullmore et al., 1999b, Bullmore et al., 2001). Next, a cluster-level threshold was computed for the resulting 3D voxel clusters. The necessary combination of voxel and cluster-level thresholds was not assumed from theory but rather was determined by direct permutation for each dataset, giving excellent type-II error control (Bullmore et al., 1999b). Cluster mass rather than a cluster extent threshold was used to minimize discrimination against possible small, strongly responding foci of activation (Bullmore et al., 1999b).

7.2.6.3 Region of interest analysis

To more specifically focus on areas implicated in the IGT and reward/punishment processing (Li et al., 2010), additional analyses were conducted using a region of interest (ROI) approach based on *a priori* hypotheses. Search space was restricted to a single mask comprising bilateral orbitofrontal cortex, medial frontal

gyrus, inferior frontal gyrus (opercularis), inferior frontal gyrus (triangularis), insula, putamen, caudate and nucleus accumbens. Regions were extracted from the Harvard-Oxford atlas using FSL (Smith et al., 2004), nonlinearly converted from Montreal Neurological Institute (MNI) coordinates into Talairach coordinates using the MNI2TAL program (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach) and combined in XBAM. Within the mask, <1 false-positive cluster was expected with thresholds of $p<0.05$ for voxel and $p<0.03$ for cluster comparisons.

7.3 Results

7.3.1 Participant characteristics

Groups did not differ in age or IQ (Table 7.1). As expected, groups differed on SDQ total and sub-scores. *Post-hoc* tests correcting for multiple comparisons showed that all groups differed on SDQ total-scores (all $Log(BF_{10})>3$, $p<0.001$). ASD boys were more impaired on peer, pro-social and hyperactivity/inattention sub-scales compared to controls and OCD boys (all $Log(BF_{10})>4$, $p<0.001$), who did not differ. On the conduct sub-scale, ASD boys differed from controls only ($Log(BF_{10})=2.64$, $p<0.003$). On the emotion sub-scale, controls differed from ASD and OCD boys (both $Log(BF_{10})>7$, $p<0.001$), who did not differ from each other.

Table 7.1 Participant characteristics

Variables	HC (N=20) Mean(SD)	ASD (N=24) Mean(SD)	OCD (N=20) Mean(SD)	*F* test (DF)	*p*-value	Log (BF_{10})
Age (years)	15.1(2.0)	14.6(1.6)	15.7(1.4)	2.7(2,61)	0.08	-0.03
IQ	119.7(11.9)	113.1(14.3)	117.7(13.4)	1.4(2,61)	0.25	-0.99
SCQ total score (*t*-test)	2.2(2.3)	16.5(7.4)	-	8.3(42)	<0.001	17.26
SDQ total score	5.0(3.9)	19.5(6.8)	12.5(5.6)	36.2(2,61)	< 0.001	19.03
SDQ emotional distress	0.7(1.7)	4.3(2.8)	4.4(2.6)	14.6(2,61)	< 0.001	7.88
SDQ conduct	0.9(1.3)	2.6(2.2)	1.9(1.5)	5.6(2,61)	0.006	2.07
SDQ peer relations	1.6(2.5)	6.5(2.4)	3.3(3.0)	19.8(2,61)	< 0.001	11.05
SDQ hyperactive impulsive/inattentive	2.2(1.9)	6.2(2.4)	3.0(2.7)	17.9(2,61)	< 0.001	9.96
SDQ prosocial behaviour	8.6(2.4)	4.5(2.4)	7.7(2.6)	17.4(2,61)	< 0.001	9.68
ADOS communication score	-	3.6(1.2)	-	-	-	
ADOS social interaction score	-	9.0(2.3)	-	-	-	
ADOS communication+social	-	12.7(3.1)	-	-	-	
ADOS stereotypy score	-	1.5(1.5)	-	-	-	
ADI communication score	-	16.6(4.7)	-	-	-	
ADI social interaction score	-	20.0(5.3)	-	-	-	
ADI repetitive behaviour score	-	6.5(2.4)	-	-	-	
CY-BOCS total score	-	-	22.3(5.8)	-	-	
CY-BOCS – obsessions	-	-	10.8(3.6)	-	-	
CY-BOCS – compulsions	-	-	12.0(3.1)	-	-	

Abbreviations: ADI, Autism Diagnostic Interview; ADOS, Autism Diagnostic Observation Schedule; ASD, Autism Spectrum Disorder; CY-BOCS, Children's Yale-Brown Obsessive-Compulsive Scale; DF, degrees of freedom; HC, healthy controls; OCD, Obsessive-Compulsive Disorder; SD, standard deviation. Note, Log(BF_{10}) is reported for Bayesian analyses, as BF_{10} values were consistently high.

7.3.2 Performance data

Groups did not differ on their preference ratio for safe decks across the entire task (BF_{10}=0.16, F(2,63)=.65, p=.53) or in group-by-block (4 blocks of 20 trials each) interaction analysis (BF_{10}=0.01, F(2,62)=0.35, p=0.71), with strong evidence in favour of the null hypothesis (BF_{01}=219.05). Task performance is illustratively summarized in Figure 7.2 and Figure 7.3.

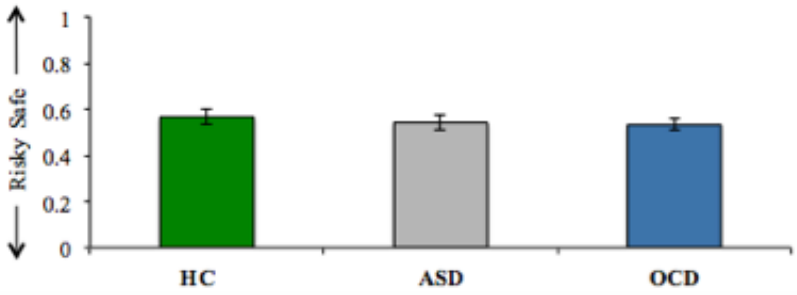


Figure 7.2 Overall advantageous preference ratios by group

Values above 0.5 denoted overall preference towards safe (advantageous) decks, whereas values below 0.5 denoted overall preference towards risky (disadvantageous) decks.

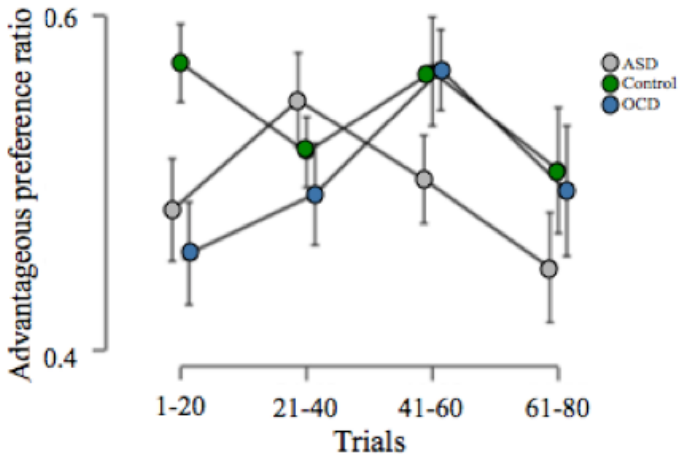


Figure 7.3 Advantageous preference ratios by task block (20 trials per block)

7.3.3 Model comparison

We first tested which model provided the best fit for the data by comparing WAIC scores (Table 7.2), with lower WAIC scores indicating better model-fits. Results suggested that the VPP model ($WAIC_{total}$=11387.78) provided the best model-fit relative to the other two models (PVL-DecayRI $WAIC_{total}$=12502.34; PVL-Delta $WAIC_{total}$=12812.60) in all three groups, consistent with previous studies (Worthy et al., 2013a, Ahn et al., 2014).

Table 7.2 WAIC scores for each model implemented in *hBayesDM*

Model	$WAIC_{HC}$	$WAIC_{ASD}$	$WAIC_{OCD}$	$WAIC_{SUM}$
PVL-DecayRI	4025	4502	3975	12502
PVL-Delta	4075	4676	4061	12813
VPP	3616	4130	3642	11388

Abbreviations: ASD, Autism Spectrum Disorder; HC, Healthy Controls; OCD, Obsessive-Compulsive Disorder; PVL, Prospect Valence Learning; RI, Reinforcement Learning; VPP, Value-Plus-Perseverance

We used the winning VPP model to compare parameter estimates among groups (Table 7.3). Controls showed greater choice sensitivity (c) compared to ASD (95% HDI from 0.83 to 4.54, mean of HDI=2.69; $t(20.4)=32.93$, $p<0.001$) and OCD boys (95% HDI from 1.44 to 4.22, mean of HDI=2.83; $t(19.2)=34.19$, $p<0.001$). Controls also showed higher reinforcement learning weights (ω) than ASD (95% HDI from 0.46 to 0.98, mean of HDI=0.72; $t(23.6)=26.13$, $p<0.001$) and OCD boys (95% HDI from 0.45 to 0.97, mean of HDI=0.71; $t(20.2)=39.96$, $p<0.001$). ASD boys showed greater perseverance decay rates (k) compared to controls (95% HDI from -0.44 to -0.06, mean of HDI=-0.25; $t(33.8)=-5.21$, $p<0.001$) and OCD boys (95% HDI from 0.005 to 0.47, mean of HDI=0.24; $t(42)=3.75$, $p=0.001$). A complete table of differential distributions is presented in Table 7.4.

Table 7.3 Parameter estimates from the VPP model

Parameter	HC (N=20) mean (SD)	ASD (N=24) mean (SD)	OCD (N=20) mean (SD)
Learning rate (*A*)	0.01 (0.01)	0.44 (0.22)	0.24 (0.15)
Feedback sensitivity (*α*)	0.14 (0.06)	0.61 (0.13)	0.96 (0.43)
Choice sensitivity (*c*)	3.16 (0.33)	0.72 (0.07)	0.66 (0.02)
Loss aversion (λ)	0.22 (0.08)	4.70 (1.65)	4.91 (2.27)
Loss impact (ε_p)	-1.38 (0.87)	-1.69 (2.97)	-1.80 (1.16)
Gain impact (ε_n)	-0.84 (1.33)	-0.76 (2.75)	-1.07 (2.16)
Perseverance decay rate (*k*)	0.42 (0.08)	0.63 (0.17)	0.44 (0.16)
Reinforcement learning weight (ω)	0.94 (0.01)	0.25 (0.13)	0.26 (0.08)

Abbreviations: ASD, Autism Spectrum Disorder; HC, healthy controls; OCD, Obsessive-Compulsive Disorder; SD, standard deviation; VPP, value-plus-perseverance

Table 7.4 Differential distributions of VPP model parameters: Highest Density Intervals for two-way comparisons

Parameter	95% HDI of MCMC	
HC vs. ASD		
A	-0.922	0.004
α	-1.775	0.181
c	0.832	4.539
λ	-9.377	0.031
ε_p	-2.105	1.329
ε_n	-1.663	1.289
k	-0.442	-0.061
ω	0.461	0.981
HC vs. OCD		
A	-0.494	0.016
α	-1.923	0.031
c	1.436	4.217
λ	-9.328	0.025
ε_p	-1.278	1.850
ε_n	-1.249	1.516
k	-0.220	0.211
ω	0.455	0.974
ASD vs. OCD		
A	-0.282	0.900
α	-1.708	1.064
c	-0.640	1.622
λ	-7.999	7.165
ε_p	-1.135	2.265
ε_n	-1.227	1.995
k	0.005	0.468
ω	-0.394	0.357

Abbreviations: α , outcome sensitivity; *A*, learning rate; ASD, Autism Spectrum Disorder; c, consistency/choice sensitivity; ε_p /ε_n, impact of gain/loss, respectively, on perseverance behaviour; HC, Healthy Control; HDI, highest density interval; *k* , perseverance decay rate; λ, loss aversion; MCMC, Markov Chain Monte Carlo sampling; OCD, Obsessive-Compulsive Disorder; ω, reinforcement learning weight

7.3.4 Movement

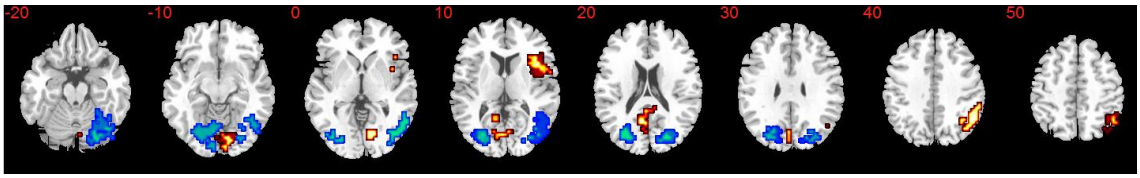
Groups did not significantly differ on minimum (BF_{10}=0.13, F(2,63)=0.03, p=0.97), maximum (BF_{10}=0.36, F(2,63)=1.37, p=0.26) or mean (BF_{10}=0.19, F(2,63)=0.49, p=0.61) head-translation in 3D-Euclidian space.

7.3.5 Group maps of brain activation

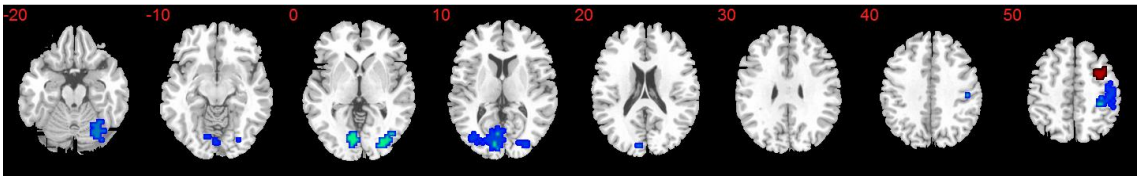
Images of within-group brain activation for task phases of choice (risky vs. safe), anticipation, and outcome (win vs. loss) are presented in Figure 7.4.

Figure 7.4.1 – Within-group maps for choice phase (red: risky>safe, blue: safe>risky)

(A) Healthy Control Boys



(B) ASD Boys



(C) OCD Boys

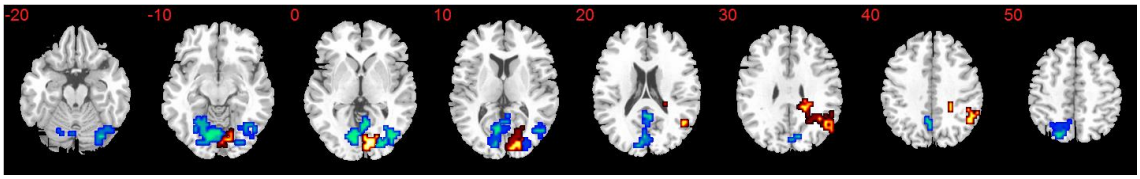
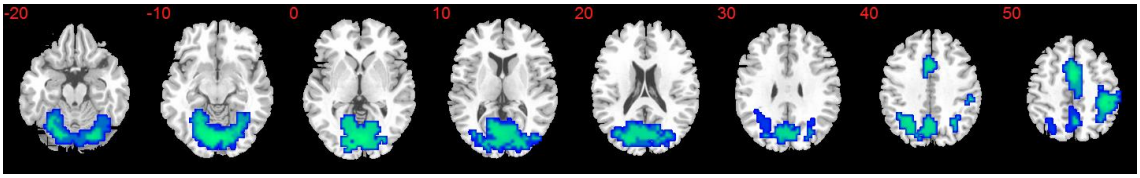
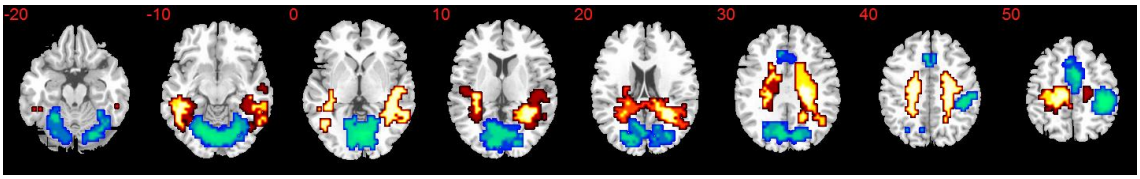


Figure 7.4.2 – Within-group maps for anticipation phase (anticipation>baseline; red: increased, blue: decreased)

(A) Healthy Control Boys



(B) ASD Boys



(C) OCD Boys

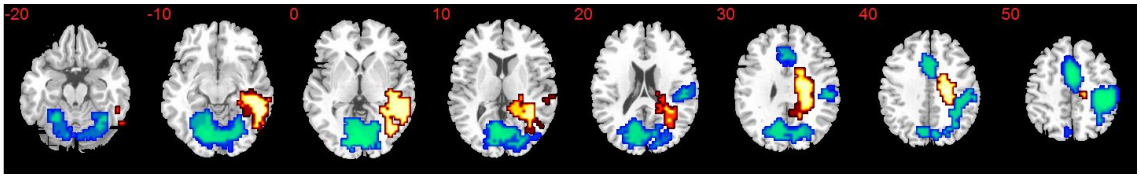
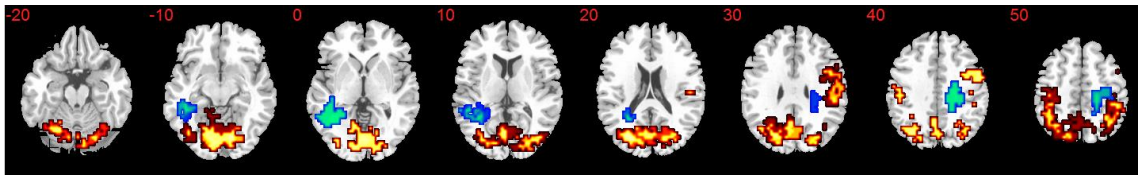
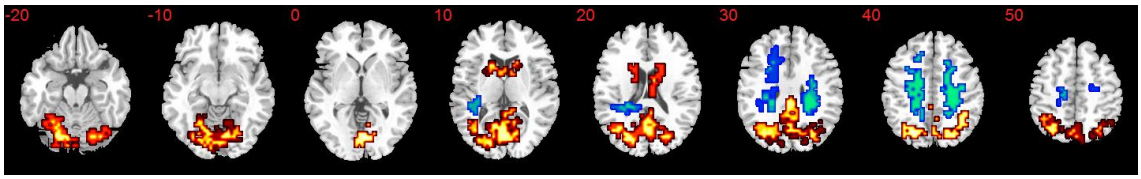


Figure 7.4.3 – Within-group maps for outcome phase (red: win>loss, blue: loss>win)

(A) Healthy Control Boys



(B) ASD Boys



(C) OCD Boys

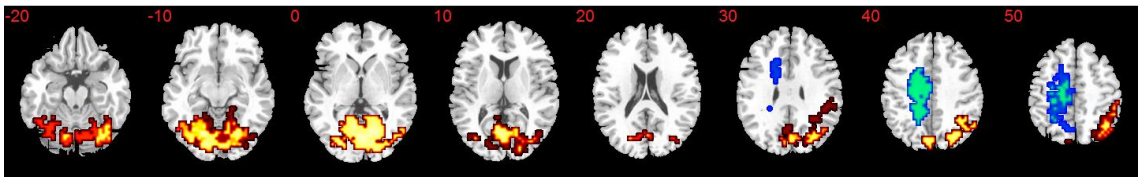


Figure 7.4 Within-group brain activation for each task condition (choice, anticipation, outcome)

(A) Healthy control boys, (B) boys with ASD, (C) boys with OCD. Talairach *z*-coordinates are shown for slice distance (in mm) from the intercommisural line. The right side of the image corresponds with the right side of the brain.

7.3.6 Group effect-choice

Whole-brain analysis of covariance (ANCOVA) including age as covariate compared brain activation during the choice phase (risky vs. safe choices) and showed a main effect of group in left DLPFC extending into superior frontal gyrus (Table 7.5A; Figure 7.5A). *Post-hoc* comparisons revealed that this was due to controls activating this region more during risky choices relative to both ASD (BF_{10}=82.98, p<0.001) and OCD subjects (BF_{10}=13.97, p=0.02).

When the search space was constrained to the fronto-striatal ROIs, controls had increased activation to risky choices relative to ASD (BF_{10}=2.83,p=0.03) and OCD (BF_{10}=7.89,p=0.005) boys in right IFG/insula (Table 7.5A; Figure 7.5B). No group differences were observed in any of the other ROIs.

Excluding the 4 medicated OCD boys from analyses had no effect on the main findings.

Table 7.5 ANCOVA results of brain activation differences between healthy control boys, boys with ASD, and boys with OCD

Contrast	Regions of activation	Brodmann areas	Peak Talairach coordinates (x,y,z)	Voxels	Cluster *p*-value
(A) Choice (risky-safe)					
Whole-brain					
HC>ASD,OCD	**L DLPFC**, superior frontal gyrus	6/8/9/46	-33,4,64	302	0.004
ROI					
ASD,OCD>HC	**R IFG**, insula	45	36,22,4	51	0.009
(B) Anticipation (vs. baseline)					
Whole-brain					
HC>ASD,OCD	**L IFG,** insula, inferior temporal	47	-40,26,-7	198	0.01
HC>ASD,OCD	**L pre**/postcentral, PCC	6	-36,-15,26	225	
ROI					
HC>ASD,OCD	**L IFG,** insula, VLPFC, OFC	47	-40,26,-13	83	0.006
HC>ASD,OCD	**R VS,** NAcc, caudate, putamen	-	7,4,-7	58	0.01
(C) Outcome (win-loss)					
Whole-brain	*No suprathreshold clusters*				
ROI					
ASD>HC,OCD	**L IFG**/insula	45/47	-33,30,-13	39	0.02

Abbreviations: ACC, anterior cingulate cortex; ASD, Autism Spectrum Disorder; DLPFC, dorsolateral prefrontal cortex; HC, healthy controls; IFG, inferior frontal gyrus; L, left; OCD, obsessive-compulsive disorder; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; ROI, region of interest; VLPFC, ventrolateral prefrontal cortex; VS, ventral striatum. **BOLD** regions=cluster-peak

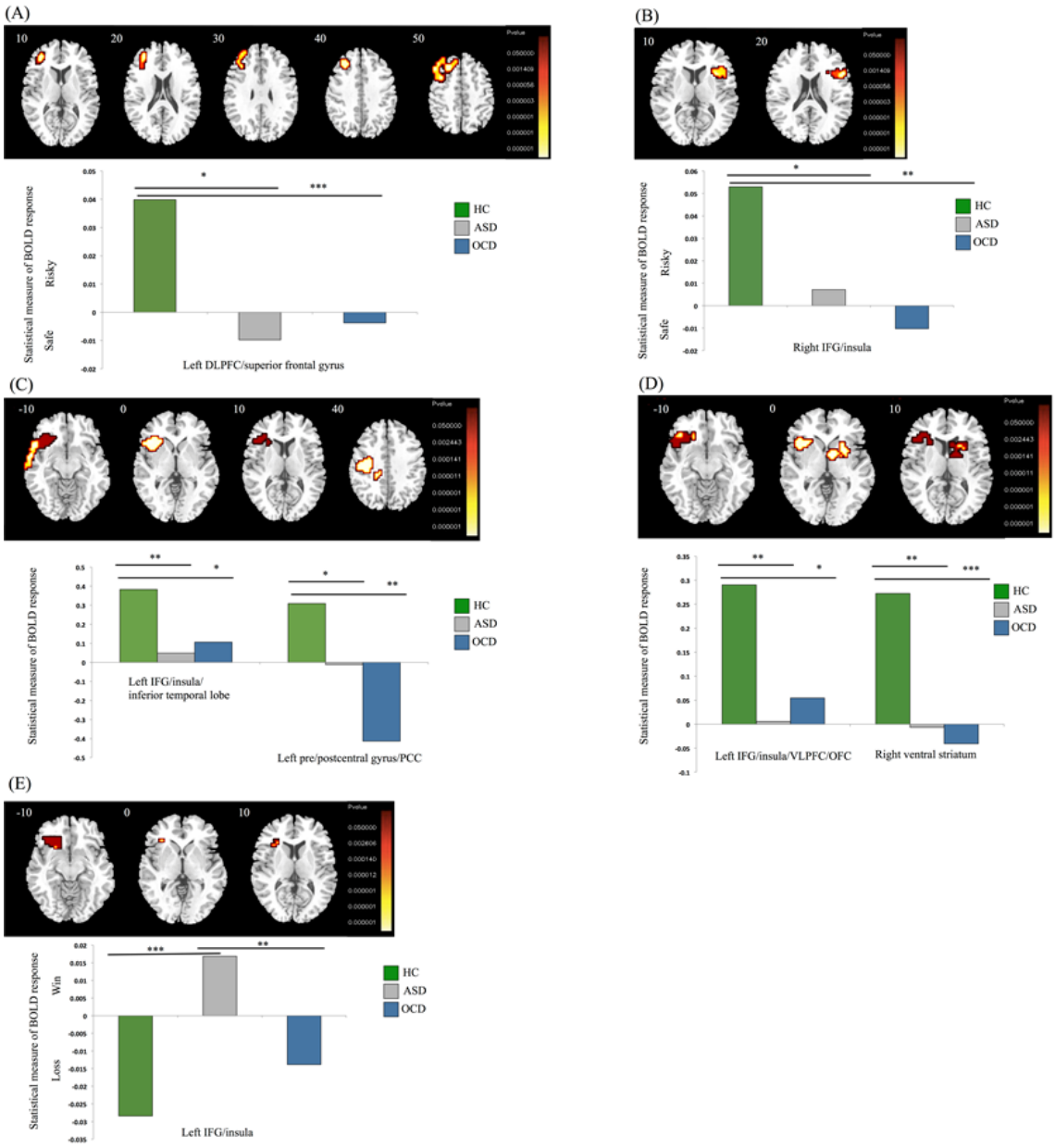


Figure 7.5 Between-group differences in brain activation between healthy control boys, boys with autism spectrum disorder (ASD) and boys with obsessive-compulsive disorder (OCD)

Analysis of variance (ANOVA) showing the main effect of group on brain activation for the three phases of the Iowa Gambling Task. (A) Whole-brain results of the group effect during decision-making (choice phase, safe vs. risky), (B) Region of interest (ROI) results of the group effect during decision-making (choice phase, safe vs. risky), (C) Whole-brain results of the group effect during outcome anticipation, (D) ROI results of the group effect during outcome anticipation, (E) ROI results of the group effect during outcome presentation (win vs. loss). Talairach z-coordinates are shown for slice distance (in mm) from the intercommissural line. The right side of the image corresponds with the right side of the brain. * indicates significance at the $p<0.05$ level, ** indicates significance at the $p<0.01$ level, *** indicates significance at the $p<0.001$ level. See Appendix B for graphs including standard error bars.

7.3.7 Group effect-anticipation

Whole brain ANCOVA comparing brain activation during outcome anticipation showed a group-effect in two regions: left IFG/insula/inferior temporal lobe and left pre/post-central gyrus extending into PCC. This was due to shared underactivation in both regions in ASD (left IFG/insula/inferior temporal lobe: BF_{10}=164.47, p=0.003; pre/postcentral gyrus/PCC: BF_{10}=5.25, p=0.05) and OCD boys (left IFG/insula/inferior temporal lobe: BF_{10}=8.29, p=0.04; pre/postcentral gyrus/PCC: BF_{10}=55.60, p=0.002) relative to controls (Table 7.5B; Figure 7.5C).

ROI analysis revealed two clusters that significantly differed among groups, one of which was observed in the whole-brain analysis (see above): left IFG/insula, extending in the ROI analysis into VLPFC/OFC, and in right ventral striatum (VS), including nucleus accumbens, caudate and putamen. Post-hoc comparisons showed shared reduction in both clusters in ASD (IFG/insula/OFC: BF_{10}=79.65, p=0.002; VS: BF_{10}=101.61, p=0.004) and OCD (IFG/insula/OFC: BF_{10}=7.82, p=0.04; VS: BF_{10}=122.07, p<0.001) boys versus controls (Table 7.5B; Figure 7.5D).

When the 4 medicated OCD boys were excluded from analyses, all group-difference clusters remained, but the difference in the right VS cluster from the ROI analysis was observed only at a reduced threshold of p=0.07 in patients relative to controls.

7.3.8 Group effect-outcome

Whole-brain analyses comparing activation differences during outcome presentation showed no effect of group when wins vs. losses were contrasted. However, ROI analysis revealed a group effect in the left IFG/insula, which was due to ASD boys having disorder-specific enhanced activation to wins relative to controls (BF_{10}=237.61,

p<0.001) and OCD boys (BF_{10}=31.60, p=0.003), who had more activation in this region to losses relative to ASD boys (Table 7.5C; Figure 7.5E). Excluding the 4 medicated OCD boys had no effect on the main findings.

7.3.9 Associations between symptom measures and task performance/brain activation

There was no relationship between symptom measures and any parameter estimate or overall advantageous preference ratio in the ASD or OCD group. There was no statistically significant correlation between symptom measures and brain activation among ASD or OCD boys.

7.3.10 Associations between task performance and brain activation

In the control group, higher advantageous preference ratios were associated with increased activation to risky vs. safe choices in left DLFPC (r=0.43, BF_{10}=7.99, p=0.007), and with increased activation during outcome anticipation in left IFG (r=0.45, BF_{10}=11.12, p=0.005)[2].

Parameter estimates or overall performance were not associated with brain activation in ASD or OCD boys.

7.4 Discussion

This is the first study to investigate the underlying neural correlates of IGT performance both in ASD and OCD and the first study to compare the two disorders in fMRI during decision-making. Individuals with ASD and OCD used different decision-making strategies with regard to decreased choice consistency and reliance on

[2] Formal comparisons of correlations between groups using Fisher's r-to-z transformation are reported in Appendix C

reinforcement learning, that were moreover different to controls, in order to achieve overall similar task performance. Furthermore, ASD and OCD boys showed shared neurofunctional underactivation relative to controls during decision-making in left dorsolateral prefrontal and right inferior fronto-insular regions and in lateral inferior/orbito-fronto-striatal regions and PCC during outcome anticipation. During outcome presentation, however, ROI analyses showed that ASD boys had disorder-specific enhanced activation to wins vs. losses in a left inferior fronto-insular region relative to OCD boys and controls.

The computational modelling results suggest that, despite overall comparable performance to controls, ASD and OCD boys used different decision-making strategies to achieve this performance. OCD and ASD participants were less consistent in their choices, in line with previous evidence of increased switching behaviour on the IGT in ASD adolescents (Johnson et al., 2006, Yechiam et al., 2010). The present work extends this evidence to OCD, suggesting that increased exploration (independent of outcome sensitivity) may be a shared trans-diagnostic behavioural phenotype of decision-making. Moreover, the finding of lower reinforcement learning weights in both patient groups compared to controls suggests that ASD and OCD individuals less effectively implemented reversal learning strategies to maximise outcomes and instead used a different strategy (e.g. exploration), in line with impaired reward learning in OCD (Nielen et al., 2009) and ASD (Scott-Van Zeeland et al., 2010b). Taken together, this suggests that patients may achieve performance similar to controls via enhanced exploration and less reliance on learning from experienced outcomes. Moreover, perseverance strengths decayed at a faster rate in the ASD group compared to the OCD and control groups, in line with evidence that ASD individuals have a disorder-specific tendency to switch decks more frequently (Johnson et al., 2006). This effect may be dissociable from the disorder-shared decreased choice consistency that was also

observed in OCD, as choices on previous decks have less influence on future choices, regardless of reward/punishment valuation on a given deck.

Whole-brain fMRI analysis results showed that both patient groups shared reduced activation in left DLPFC during decision-making relative to controls and these results were extended to the right IFG/insula in ROI analyses. Lateral PFC is important for value representation (Ridderinkhof et al., 2004), and more specifically, DLPFC has been implicated in working memory, important for incorporating known information during decision deliberation (Li et al., 2010). DLPFC activation during decision-making under ambiguity is typical in healthy populations (Krain et al., 2006). Moreover, ventrolateral prefrontal regions and the insula are related to emotional attribute of decision options and are part of a 'saliency' network implicated in stimulus significance and affective response (Phillips et al., 2003). IGT performance and neural representation of decision values in dorso- and ventrolateral PFC mature with age, suggesting development of a decision-making network incorporating action values with executive processes (Christakou et al., 2013a). Thus, the present findings could imply abnormalities in the functional maturation of these regions in ASD and OCD. Furthermore, enhanced activation in left DLPFC and right IFG/insula to risky vs. safe decks was related to better performance in controls, whereas this relationship in the DLPFC was not seen in ASD or OCD individuals. Given the DLPFC's role in integrating memory representations with goal-directed behaviour (Ridderinkhof et al., 2004), this may suggest that ASD and OCD individuals have neurofunctional deficits in updating reward expectation. Moreover, in ASD, reduced DLPFC activation has been found during reversal learning, suggesting that abnormalities in this region may relate to problems in flexibly updating choice behaviour (D'Cruz et al., 2016).

Whole-brain results showed that both patient groups relative to controls had reduced activation in left OFC/VLPFC/IFG/insula during outcome anticipation. In ROI

analyses, these results were confirmed as well as extended to right BG/VS. This is in line with evidence in OCD of decreased lateral orbitofrontal activation during outcome presentation on a reversal-learning task (Remijnse et al., 2006, Chamberlain et al., 2008) and reward anticipation (Jung et al., 2011) and extends this evidence to ASD. In OCD, OFC deficits have been linked to impaired reward-related learning and to an inability to detect changes in reinforcement contingencies (Menzies et al., 2008), and the present findings suggest that this phenotype may be shared with ASD, in line with evidence in ASD of fronto-limbic abnormalities during reward gain/loss, independent of valence (Kohls et al., 2013). Moreover, cognitive inflexibility has been associated with OCD, affecting goal-directed decision-making and learning (Gillan and Robbins, 2014). A previous study found that OCD adolescents had reduced left IFG activation compared to controls during set-shifting (Britton et al., 2010). Moreover, a study of reward reversal-learning found that ASD adults had reduced VS as well as left DLFPC and parietal activation compared to controls (D'Cruz et al., 2016), in line with our findings of disorder-shared reduced activation in these regions, implicating these areas in a range of reward-related processes that may be affected in both ASD and OCD.

The BG, and more specifically the caudate and VS, have been consistently implicated in reward expectation and value representation (Dichter et al., 2012a). This region is particularly relevant to OCD given the prominence of fronto-striatal networks in the neurofunctional characterization of the disorder (Menzies et al., 2008). ROI findings of disorder-shared blunted VS response during reward anticipation are in line with previous findings of similar underactive VS response during ambiguous reward anticipation in ASD (Dichter et al., 2012b, Kohls et al., 2013, D'Cruz et al., 2016) and OCD (Menzies et al., 2008, Figee et al., 2011) as well as depression (Smoski et al., 2009) and schizophrenia (Juckel et al., 2006), suggesting the possibility of a shared

neurobiology among a range of disorders with regard to fronto-striatal under-responsiveness to anticipated reward.

ROI analyses revealed that ASD boys had disorder-specific increased activation in left IFG/insula to positive (wins) vs. negative (losses) feedback relative to OCD boys and controls, who both had more activation to loss in this region. Some studies have found insula hyperactivation during reward in ASD (Cascio et al., 2012b, Dichter et al., 2012d), and another found enhanced left frontal activation in ASD individuals during rewarded outcomes (Schmitz et al., 2008), implying that reward-related left-frontal systems are enhanced in ASD (Cascio et al., 2012b). This is in line with the insula's role in interoceptive awareness as part of the proposed 'saliency network' (Critchley et al., 2004, Menon and Uddin, 2010), suggested to be affected in ASD individuals (Uddin and Menon, 2009), and suggests that similar systems are intact in OCD patients during reward processing.

This study has several limitations. While psychiatric comorbidity was an exclusion criterion, we cannot discard the possibility that sub-threshold symptoms of other disorders were present in our sample. Moreover, ASD participants were not assessed using OCD-specific measures, e.g. CY-BOCS, (and vice-versa). Nonetheless, thorough clinical assessment of ASD and OCD participants and inclusion of mostly medication-naïve patients are study strengths, and absence of comorbidity was confirmed by a consultant psychiatrist in all cases. Four OCD boys were prescribed SSRIs. Although there is evidence for neurofunctional effects of serotonin during decision-making (Murphy et al., 2008), results largely remained when medication was accounted for. However, the right VS cluster was seen only at a reduced threshold, suggesting a possibility that medication may have influenced brain activation during reward anticipation in this region. However, it is more likely that this secondary analysis was underpowered. Moreover, we found no association between symptom

severity and performance measures, which is possibly due to patient/symptom heterogeneity in our clinical groups.

7.5 Conclusions

This first behavioural and fMRI comparison of ASD and OCD adolescents on the IGT showed that ASD and OCD patients used different decision-making strategies relative to controls in that they were less consistent in their choices and relied less on reinforcement learning to achieve overall performance comparable to controls. ASD adolescents, moreover, had distinctive perseverative task performance. This was underpinned by predominantly shared neurofunctional deficits relative to controls in dorsal and ventral prefrontal regions during decision making and in orbitofrontal-ventral striatal regions during reward and loss processing, as shown by both whole-brain and ROI analyses. ASD patients, however, had disorder-specific enhanced inferior frontal/insular activation to reward feedback in the ROI analysis, suggesting a possible neurofunctional signature of reward-based decision-making on the IGT that may be unique to ASD. This study provides novel insight into underlying neurobiological and behavioural mechanisms that shed light on trans-diagnostic phenotypes of reward-learning and decision-making that may drive respective clinical characteristics of executive impairments in each disorder.

CHAPTER 8 - GENERAL DISCUSSION

8.1 Summary

ASD and OCD are two disorders that commonly emerge in early childhood or adolescence (Ruscio et al., 2010, Russell et al., 2016), are frequently co-morbid with one another (Leyfer et al., 2006, Doshi-Velez et al., 2014, Murray et al., 2015) and exhibit deficits in executive function, both at a behavioural and neurobiological level (Mataix-Cols et al., 2005, Fineberg et al., 2009, Anholt et al., 2010). However, the shared and disorder-specific neurostructural and neurofunctional underpinnings of cognitive and behavioural impairments in these disorders had yet to be investigated prior to the studies outlined in this thesis. These studies have, for the first time, 1) used comparative multi-modal meta-analytic methods to compare overlap and disorder-specificity in brain structure and brain function deficits during cognitive control between individuals with ASD and OCD and 2) used fMRI to directly compare adolescent boys with ASD and with OCD during cognitive tasks of cool and hot EF including sustained attention, temporal discounting and gambling. The results show both shared and disorder-specific structural and functional brain abnormalities between ASD and OCD.

The meta-analysis findings show that in structure and in function during inhibitory control, both disorders shared reductions in r/dACC/MPFC relative to control groups, presumably reflecting reduced top-down cognitive control over affective systems. The most prominent disorder-specific finding was that OCD patients had increased GMV and function during inhibitory control in left putamen and insula compared to controls and ASD individuals, in line with theories of fronto-striatal dysregulation in OCD (Menzies et al., 2008). Moreover, in the VBM analysis, findings in right striato-insular regions were disorder-dissociated such that GMV was increased

in OCD but decreased in ASD relative to control groups. Other disorder-dissociated effects were observed in left superior frontal gyrus, which was reduced in volume in OCD but enhanced in ASD relative to control groups. OCD patients had disorder-specific right superior temporo–parietal underfunctioning relative to ASD and control groups, presumably reflecting problems with recruiting posterior attention systems. ASD-specific findings were observed in left DLPFC, which was reduced, and in PCC/precuneus, which was enhanced in activation compared to OCD patients and controls, suggesting increased deficits deactivating default mode regions during cognitive tasks as well as lateral prefrontal executive attention abnormalities.

The experimental fMRI studies found both shared and disorder-specific deficits between boys with ASD and with OCD. During sustained attention, ASD boys did not differ from OCD boys on any performance measures, and neither clinical group differed from controls. However, there were differences in neurofunctional activation patterns. OCD boys had disorder-specific reduced activation in inferior-fronto-insular and temporo-parietal regions relative to ASD boys and controls, in line with disorder-specific reductions in temporo-parietal regions during cognitive control as shown in the meta-analysis. The findings suggest OCD-specific abnormalities during cool EF in temporo-parietal attention as well as salience detection networks. OCD boys also had disorder-specific increased activation with increasing delay in rMPFC, possibly relating to increased performance monitoring. Both ASD and OCD individuals shared increased activation with increasing delay in cerebellar/occipital attention regions compared to controls, with significant shared case-control differences in all delay conditions, implicating cerebellar dysfunction as a possible shared phenotype in the context of attention and cool EF.

During TD, ASD boys had disorder-specific impaired task performance; ASD boys discounted rewards more steeply than OCD boys and controls, who did not differ

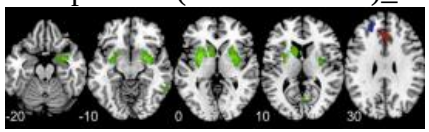
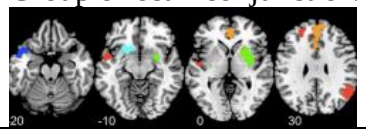
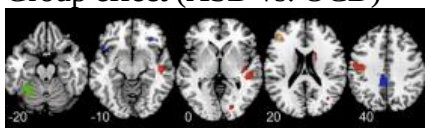
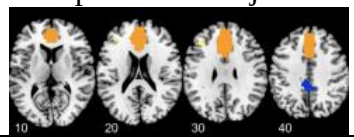
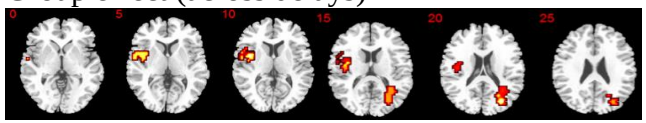
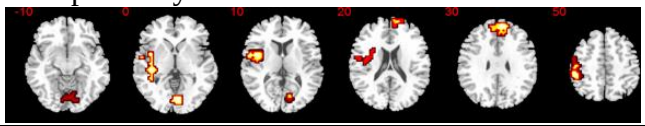
from one another. However, despite this ASD-specific performance impairment, fMRI results showed predominantly shared neurofunctional abnormalities in both ASD and OCD boys relative to controls. Disorder-shared deficits were seen in ventral and lateral prefrontal regions, where ASD and OCD boys had increased activation to immediate versus delayed choices, but controls had more activation to delayed versus immediate choices, suggesting shared impairments in the neural underpinnings of planning and successful reward-based decision-making. Other shared findings were observed in the cerebellum and PCC, where both patient groups had reduced activation to delayed versus immediate choices compared to the control group, and in ventromedial orbitofronto-striatal and bilateral medial and superior temporo-parietal regions, where both patient groups had decreased activation to immediate versus delayed choices relative to the control group, which had enhanced activation. Moreover, in the medial orbitofronto-striatal regions, there was a trend toward slightly more reduced activation in the ASD compared to the OCD group. These findings are in line with ventromedial prefrontal abnormalities commonly observed in ASD during hot EF, especially in tasks involving monetary reward (Schmitz et al., 2008, Dichter et al., 2012b, Dichter et al., 2012d, Kohls et al., 2013), and extend these results to OCD individuals, alongside frontal functional abnormalities in ventromedial and orbitofrontal regions (Menzies et al., 2008, Brem et al., 2012). Moreover, the findings of shared temporo-parietal abnormalities in the context of hot EF are in contrast to those during cool EF, where temporo-parietal reductions were disorder-specific to OCD.

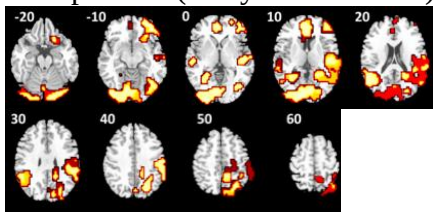
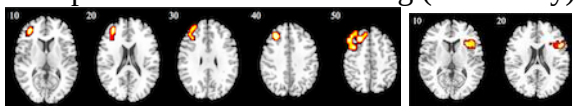
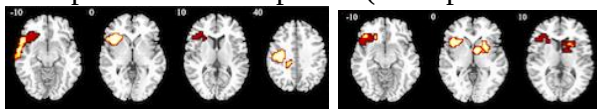
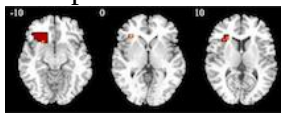
During the IGT, groups did not differ on the proportion of advantageous/safe choices they made across the task. However, when computational models of decision-making were fit to the performance data, results from the winning model showed that ASD and OCD boys shared reduced choice sensitivity as well as lower reinforcement learning rates relative to controls, suggesting shared differences between patients in

nuanced aspects of decision-making styles that lead to overall task performance comparable to controls. Disorder-specific performance effects were observed in ASD individuals, who had greater perseverance strength decay rates compared to the OCD and control groups. fMRI results showed that during the decision-making phase of the task, ASD and OCD boys both had less activation during risky compared to safe choices relative to control boys in left DLPFC. ROI analysis of fronto-striatal regions during decision-making showed additional disorder-shared abnormalities in right inferior fronto-insular regions, where both clinical groups compared to controls had less activation to risky choices. Whole-brain fMRI of outcome anticipation also revealed disorder-shared dysfunction in inferior fronto-temporal and fronto-parietal regions, where patients had underactivation relative to controls. ROI analysis extended these results to key reward-related ventrolateral and orbitofronto-striatal regions. ROI analysis also showed a disorder-specific effect in ASD boys during outcome presentation in left IFG/insula, in line with findings of increased left inferior fronto-insular activation in ASD individuals during reward receipt (Schmitz et al., 2008, Cascio et al., 2012a).

The findings of each of these studies is summarised in Table 8.1 and will be discussed in detail below to consider shared and disorder-specific abnormalities in boys with ASD and OCD.

Table 8.1 Summary of main study results

Task/study	ASD-specific	OCD-specific	Disorder-shared	Contrast images
Meta-analysis (VBM) *reported findings are only those that survived matched subgroup analyses	↓right BG/insula ↑left superior frontal	↑bilateral BG/insula	↓r/dACC/MPFC	Group effect (ASD vs. OCD)_  Group effect – conjunction/disjunction (ASD+OCD) 
Meta-analysis (cognitive control) *reported findings are only those that survived matched subgroup analyses	↓left DLPFC ↑PCC/precuneus	↓right MTL/STL ↓PCC/precuneus	↓r/dACC/MPFC	Group effect (ASD vs. OCD)  Group effect – conjunction/disjunction (ASD+OCD) 
Sustained attention	None observed	(Group effect) ↓left insula/IFG ↓right PCC, STL (Group x delay) ↓left IFG/insula, ↓IPL ↑rMPFC	(Group x delay) ↑cerebellar vermis /occipital	Group effect (across delays)  Group x delay interaction 

Temporal discounting	Steeper temporal discounting behaviour	None observed	(Delay): ↓right vmOFC/VLPFC ↓lateral cerebellum ↓PCC/precuneus (Immediate): ↓ACC/vmPFC ↓left caudate ↓bilateral inferior temporo-parietal	Group effect (delay > immediate) 
Iowa Gambling Task	↑perseverance decay rates (Outcome): ↑left OFC/IFG/insula	None observed	↓choice consistency ↓RL weight (Decision-making): ↓left DLPFC ↓right IFG/insula/OFC (Anticipation): ↓left OFC/VLPFC, VS	Group effect – decision-making (safe>risky)  Whole-brain ROI Group Effect – anticipation (anticipation>baseline)  Whole-brain ROI Group effect – outcome (win>loss)  ROI

Abbreviations: ACC, anterior cingulate cortex; ASD, autism spectrum disorder; BG, basal ganglia; DLPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; IPL, inferior parietal lobe; MPFC, medial prefrontal cortex; MTL, medial temporal lobe; OCD, obsessive-compulsive disorder; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; PFC, prefrontal cortex; r/d, rostral/dorsal; ROI, region of interest; STL, superior temporal lobe; VLPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex; vmOFC, ventromedial orbitofrontal cortex; VS, ventral striatum

8.2 Meta-analytic comparison of brain structure and function during cognitive control tasks

This section will focus on the meta-analytic findings of similarities and differences in voxel-wise volumetric differences in grey matter as well as in functional brain activation during tasks of cognitive control between adults and children with ASD and OCD.

GMV results within each patient group separately confirmed findings of previous reviews and meta-analyses (Radua and Mataix-Cols, 2009, Radua et al., 2010, Cauda et al., 2011, Nickl-Jockschat et al., 2012, Peng et al., 2012, Eng et al., 2015, Ha et al., 2015). Among ASD studies, ASD individuals relative to typically-developing controls had reduced GMV in medial prefrontal-insular and cerebellar regions including r/dACC/MPFC, right posterior insula and left cerebellum. ASD individuals also had enhanced GMV in fronto-temporo-parietal regions including left middle and superior temporal lobes, right IPL/occipital lobe, left MFG, bilateral precentral gyri and right inferior temporal gyrus. Among OCD studies, patients relative to controls had decreased GMV in medial and ventrolateral prefrontal regions including a large cluster comprising v/r/dACC/MPFC and in left VLPFC extending into premotor cortex and increased GMV in bilateral striato-thalamic and limbic regions including putamen, caudate, NAcc and pallidum, bilateral amygdala and insula, and in cerebellum, left postcentral gyrus, and right superior parietal lobe. These results support evidence of fronto-temporo-parietal and fronto-limbic structural abnormalities in ASD (Nickl-Jockschat et al., 2012, Ha et al., 2015) and CSTC structural abnormalities in OCD (Mataix-Cols et al., 2005, Menzies et al., 2008, Radua et al., 2010). However, the largest and most recent meta- and mega-analysis of sMRI data across children and adults with OCD (ENIGMA consortium, N=1,830 OCD patients; (Boedhoe et al., 2017)) suggested that many of the commonly reported subcortical structural abnormalities in OCD may be significantly

related to age, medication status or illness duration. For example, this study found increased thalamic GMV only when comparing unmedicated children, but not adults, with OCD to control children. This same study also found reduced hippocampal volumes and enhanced pallidum volumes only in adults with OCD and showed that these differences were related to lifetime history of depression. These implications of age-related abnormalities are especially important to keep in mind when interpreting the results of the present meta-analysis, which included both children and adults.

However, the primary aim of this meta-analysis was to directly compare ASD and OCD. When both GMV and functional activation were compared between studies in ASD and studies in OCD relative to respective control groups, the most prominent finding was a shared reduction in both groups in overlapping MPFC/dACC regions. Medial prefrontal cortical regions including the rostral and dorsal ACC are critically important in the successful control of systems of affect and motivation and are closely connected with other medial prefrontal regions (MacDonald et al., 2000, Goodkind et al., 2015). Reduced GMV and activation in these regions during a range of executive and affective processes has been observed in meta-analyses across a number of psychiatric disorders including schizophrenia, bipolar disorder, anxiety, depression, OCD and conduct disorder (Glahn et al., 2008, Goodkind et al., 2015, Alegria et al., 2016, Norman et al., 2016, Wise et al., 2016). While structural abnormalities alone cannot be directly linked to function or behaviour, the fact that VBM results were paralleled in the fMRI and the multi-modal analyses suggests the possibility of a trans-diagnostic neural signature of impaired top-down medial prefrontal control that is common to multiple disorders, many of which emerge in childhood and adolescence. Taken together with disorder-specific findings in OCD of enhanced striato-insular activation and volume, but disorder-specific findings of left dorsolateral prefrontal and right striato-insular reductions in ASD (discussed further below), the meta-analysis

results provide preliminary large-scale evidence for the hypothesis of fronto-striatal dysregulation in OCD but an overall reduction in activation within fronto-striatal networks in ASD, presumably underpinned in both cases by poor frontal control over striato-limbic regions that are overactive in OCD but reduced in ASD. It is interesting to note that in the OCD literature, ACC hyperactivation has also been observed, primarily in ROI fMRI studies (Ursu et al., 2003, Maltby et al., 2005, Fitzgerald et al., 2010) but also supported by a recent meta-analysis (Eng et al., 2015). However, it is likely that this overactivation (or failure of deactivation) in medial prefrontal regions is not directly linked to inhibitory control abnormalities, but rather is a result of impaired action monitoring and conflict detection that is inherent in the particular error monitoring tasks used. In conclusion, these results provide evidence for a possible trans-diagnostic functional and structural phenotype presumably reflecting impaired top-down ventromedial prefrontal and ACC-mediated control over subcortical striatal systems in both ASD and OCD.

The disorder-specific findings of enhanced bilateral striato-insular GMV paralleled by disorder-specific increased activation during cognitive control in left putamen and insula in OCD relative to ASD extends a large evidence base implicating abnormal GMV in these regions in OCD relative to controls (Radua and Mataix-Cols, 2009, Radua et al., 2010, Peng et al., 2012, Eng et al., 2015) as well as striato-insular hyperactivation including enhanced dorso-caudal and putamen-mediated sensorimotor processing and inhibitory control (van Velzen et al., 2014) and insula-mediated interoceptive dysfunction (Nagai et al., 2007). The fact that these enhanced volumes are also seen in direct comparison to ASD individuals strengthens this evidence and suggests that this may be a distinct neural signature of OCD and not ASD. However, these findings were across studies of both children and adults, as the analysis was not sufficiently powered to distinguish between paediatric and adult investigations. A recent

multi-site mega-analysis of VBM studies in OCD found that in healthy individuals, right striatal and insula volumes decreased linearly with age, while GMV in these regions was preserved across the lifespan in individuals with OCD (deWit et al., 2014). A more recent ROI-based meta- and mega-analysis found GMV deficits in subcortical striatal regions in adults with OCD but critically did not find these differences in children with OCD compared to controls, further implicating age as a possible confound in these results (Boedhoe et al., 2017). This evidence highlights the importance of age-related factors that may influence grey matter development (or indeed loss) in these regions from childhood/adolescence into adulthood, particularly in the context of disorders such as ASD and OCD that typically arise in childhood. Nonetheless, taken in conjunction with the finding of MPFC/dACC GMV reduction, these findings support theories of a disorder-specific dysregulation within fronto-striatal networks in OCD (e.g. as reviewed in (Mataix-Cols and van den Heuvel, 2006)), suggesting poor mPFC-mediated inhibition of overactive striato-thalamic regions including ventral and dorsal subdivisions of the BG that is specific to OCD, affecting motivation control, affect processing and sensorimotor processing. Ultimately, this may provide support for clinical features observed in OCD of poor control over obsessions, anxiety and compulsive behaviours.

Disorder-differentiated structural abnormalities were observed in left DLPFC, where ASD individuals had increased GMV but OCD individuals had reduced GMV compared to controls. This region was paralleled in the fMRI findings, where reduced left DLPFC activation during cognitive control was disorder-specific to ASD relative to OCD. These results are in line with previous evidence of reduced DLPFC activation in ASD individuals across a range of hot and cool EF tasks including inhibition (Kana et al., 2007), working memory (Di Martino et al., 2009, Stigler et al., 2011), reversal learning (D'Cruz et al., 2016) and attention (Silk et al., 2006, Christakou et al., 2013b).

Moreover, the DLPFC has been specifically implicated in attentional maintenance during EF (MacDonald et al., 2000), suggesting a disorder-specific abnormality in attention-related cool EF functions underpinned by reduced DLPFC reduction in ASD. The structural findings also extend theories of early brain overgrowth in ASD, as the PFC is among the first regions to develop in early childhood (Carper and Courchesne, 2005, Courchesne et al., 2007). However, these conclusions are preliminary, as this meta-analysis was conducted across child and adults studies (although more than half of the included ASD VBM studies were in children, with a mean age across all studies of 18 years). Moreover, our findings of enhanced GMV in this region in ASD corroborates evidence from a meta-analysis across children and adults with ASD which links structural alterations in this region with repetitive behaviour symptom severity (Rojas et al., 2006), suggesting that there may be clinical implications of volumetric changes in this region that are specific to the pathophysiology of ASD. It is important, however, to comment on the relationship between brain structure and function, particularly in the context of the DLPFC findings in ASD. The ASD group had enhanced GMV in this region but decreased activation relative to the OCD and control groups. Though direct links between GMV and BOLD signal have not been established, the divergent relationship between structure and function in this meta-analysis seems somewhat counterintuitive. However, it should be noted that the location of the DLPFC cluster found in the meta-analysis for structural MRI studies was not identical to the location of the DLPFC cluster in the functional MRI meta-analysis. The GMV cluster was more dorsomedial and more rostral, extending towards BA 8, whereas the fMRI cluster was more dorsolateral and caudal, extending towards BA 46. Therefore, it is possible that these sub-regions of the DLPFC are differentially implicated in structure versus function. Moreover, the functional meta-analysis was restricted to the construct of inhibitory control, and in the context of other functions the potential overlap between

structural and functional findings may well be different. Lastly, setting aside the fact that the clusters observed in these f/sMRI meta-analyses were not overlapping, while the exact relationship between GMV and BOLD signal remains to be determined, one can hypothesise that structural/functional overlap independent of direction could suggest that this region is abnormally implicated in the study population.

Disorder-specific functional effects were also observed in PCC extending into precuneus, where ASD individuals had increased activation relative to controls and OCD individuals. This result was further observed in disjunction analyses showing that this region was decreased in activation in OCD individuals relative to controls. Both the DLPFC and PCC results specific to ASD extend findings from a previous study from our group during sustained attention, where DLPFC hypoactivation and increased PCC activation, both of which were observed in ASD boys and ADHD boys relative to controls, were anti-correlated in both clinical groups (Christakou et al., 2013b). This may suggest a failure of deactivation in default-mode regions in conjunction with reduced lateral prefrontal control during cool EF. Moreover, these results show for the first time that this abnormality is disorder-specific to ASD when compared with OCD.

OCD also had disorder-specific underactivation in right superior temporal and inferior parietal regions relative to ASD and control individuals. These findings are in line with evidence of temporo-parietal underactivation during a range of hot and cool EFs including interference and response inhibition (Nakao et al., 2005, Roth et al., 2007, Woolley et al., 2008, Page et al., 2009), planning (van den Heuvel et al., 2005b), and task-switching (Menzies et al., 2008) and shows for the first time that this may be specific to OCD compared to ASD in the context of cognitive control. Moreover, this evidence provides support for a disorder-specific reduction in visual-spatial saliency processing among posterior temporo-parietal regions in OCD, particularly during non disorder-relevant EF such as inhibitory control, in contrast to the enhanced saliency

processing in similar regions that has been observed in OCD during disorder-relevant symptom provocation paradigms (Menzies et al., 2008, Rotge and Tignol, 2008). However, it is interesting to note that superior temporal and parietal hypoactivation has also been linked to ASD in the context of social communication difficulties as well as RRBIs (Adolphs, 2001, Amaral et al., 2008, Redcay, 2008, Ha et al., 2015). Therefore, it is possible that temporo-parietal underactivation is broadly implicated in lack of action control, but that abnormalities in these regions during non-social cool EF may be more specific to OCD relative to ASD.

To summarise, the findings of the VBM and fMRI meta-analysis suggest a dysregulation within medial fronto-striatal networks in OCD (decreased frontal, enhanced striatal GMV and activation) but an overall reduction within similar networks in ASD. In ASD, DLFPC GMV increases support theories of early brain overgrowth in prefrontal regions that may link to repetitive behaviours (Rojas et al., 2006). This finding was paralleled by reduced activation in this region in ASD, possibly linking to disorder-specific difficulties with dorsolateral prefrontal-mediated attentional maintenance during cool EF. Moreover, temporo-parietal underactivation was specific to OCD, suggesting a disorder-specific abnormality in posterior attention networks during cool EF. These large-scale findings provide a preliminary basis on which to examine possible biomarkers that may differentiate these disorders.

However, these abnormalities were underpinned in both cases by reduced medial prefrontal and ACC volumes and activation in both disorders relative to typically-developing individuals, which may relate to poor top-down control over subcortical and limbic regions. Based on recent meta- and mega-analyses in these disorders (e.g. (Boedhoe et al., 2017)), it is critical to keep in mind the effects that age and clinical heterogeneity may have on structural abnormalities when comparing these two

disorders, an important consideration for future research in these developmental disorders.

8.3 Experimental findings

This section will discuss the shared and disorder-specific behavioural and fMRI findings.

8.3.1 Cool EF and sustained attention

The only experimental effects specific to OCD were observed during sustained attention. In this study, boys with OCD had decreased activation across all delay conditions in key attention regions of left insula and IFG and in right PCC and STL relative to both control boys and ASD boys, who did not differ from one another. Moreover, there were significant effects of delay on brain activation in the OCD group compared to the control and ASD groups, who did not statistically differ. These disorder-specific effects were in left IFG/insula and left IPL/pre/post-central gyrus, where OCD boys had progressively reduced activation with increasing delay, and in rMPFC, where OCD boys had increased activation with increasing delay. There is support for the insula's role in saliency and timing functions (Voisin et al., 2006, Wiener et al., 2010), as well as the IFG's role in ventral attention regions important for attention orienting (Corbetta and Shulman, 2002). Moreover, there is evidence of functional maturation within inferior fronto-insular and temporo-parietal regions during sustained attention (Christakou et al., 2009b, Smith et al., 2011). The temporo-parietal findings also parallel similar findings specific to the OCD group in the fMRI meta-analysis of cognitive control studies, suggesting that this temporo-parietal underactivation is disorder-specific in the context of cool EF. Moreover, these findings could suggest a unique pattern of abnormal or delayed maturation within these networks

in OCD. The findings in rMPFC are in line with evidence of medial prefrontal hyperactivation commonly observed in OCD during attention and error monitoring (Chamberlain et al., 2005, Maltby et al., 2005, Menzies et al., 2008). Progressively enhanced rMPFC activation during sustained attention in the face of overall performance comparable to controls could suggest that OCD boys are more sensitive to time delays, allocating greater action monitoring resources over increasing time. This enhanced action monitoring could possibly relate clinically to a heightened need for things to be "just right". Taken together, the present results support previously observed patterns of reduced activation in key inferior-fronto-insular and temporo-parietal attention regions in OCD and provide first evidence of a possible neural signature specific to OCD regarding mPFC hyperactivation during cool EF tasks as well as functional maturation of lateral fronto-parieto-temporal attention networks relative to ASD. Collectively, this evidence may relate to OCD-specific clinical features of difficulty maintaining attention to relevant tasks when attentional resources are allocated towards internal thoughts and obsessions.

There were also shared activation increases between ASD and OCD boys relative to controls during sustained attention in the cerebellar vermis and occipital lobe with increasing delay. Moreover, this activation was enhanced in all delay conditions relative to controls. Cerebellar abnormalities have been widely implicated in ASD (Allen and Courchesne, 2003, Stigler et al., 2011, Wang et al., 2014), including as a disorder-specific abnormality relative to ADHD boys during sustained attention (Christakou et al., 2013b), and have also been implicated in OCD (van den Heuvel et al., 2009). The cerebellum is a key attention region, important for timing intervals (Coull, 1998) and is activated in healthy populations with increasing temporal delays, as shown by a meta-analysis of sustained attention studies in adults (Langner and Eickhoff, 2013). Interestingly, two recent studies of other attention functions (attentional capture

and spatial attention) in adolescents with ASD showed decreased cerebellar activation (Keehn et al., 2016) or increased deactivation (Rahko et al., 2016) in ASD individuals relative to typically-developing controls, suggesting that the shared overactivation observed in the present study may be specifically related to the temporal aspect of sustained attention. Therefore, shared overactivation in this region presents evidence that adolescents with ASD and OCD may share impairments in the neural mechanisms underlying vigilance to temporal delays and anticipation of motor responses underpinned by cerebellar vermis abnormalities. This extends evidence that the cerebellum is a key attention region functionally implicated in the pathophysiology of ASD (Allen et al., 1997) and presents new evidence that this neurofunctional abnormality may be shared with OCD in the context of sustaining attention across time.

Collectively, OCD had disorder-specific inferior frontal and temporo-parietal abnormalities during sustained attention, a finding which was paralleled in the meta-analysis by similar disorder-specific reductions during cognitive control. This suggests that although temporo-parietal hypoactivation has also been linked to ASD in the context of social communication difficulties (Adolphs, 2001, Amaral et al., 2008, Redcay, 2008, Ha et al., 2015), hypoactivation in these regions is specific to OCD in the context of non-emotional cool EF that may relate to temporo-parietal attention network dysfunction. Shared increases were also seen during sustained attention in the cerebellar vermis and occipital lobe, suggesting a shared mechanism for impairments in attention to temporal delays.

8.3.2 Hot EF and reward-based decision-making

During hot EF and reward-based decision-making, the ASD group had disorder-specific behavioural abnormalities on the TD and IGT tasks. Findings of steeper TD relative to OCD patients and controls links to more impulsive reward-based decision-

making that has been observed previously in young children with ASD compared to typically-developing children (Faja and Dawson, 2015). This suggests that impaired temporal foresight may be a distinct behavioural phenotype of younger individuals with ASD relative to OCD and may relate clinically to behavioural rigidity and a need for sameness, as ASD individuals are less tolerant of delays and instead prefer immediate gratification to prevent uncertainty (Boulter et al., 2014). However, other studies have shown no performance impairments during TD in adolescents with ASD (Antrop et al., 2006, Demurie et al., 2012). Thus, while the present findings support evidence for TD impairments specific to ASD relative to OCD, studies of larger, well-defined samples of ASD individuals are needed to confirm this hypothesis, as discrepancies are likely due to heterogeneity among samples of individuals with ASD.

However, despite these disorder-specific hot EF behavioural impairments, ASD-specific neurofunctional effects were observed only during ROI analyses of the outcome phase of the IGT but not during other conditions or during sustained attention or TD. These abnormalities were seen in the left IFG and insula, which were increased in activation to the presentation of reward versus loss relative to OCD and control boys and were observed only in ROI analyses. Moreover, this neurofunctional abnormality was observed alongside disorder-specific performance impairments related to perseverative choice behaviour. This is an important finding because it suggests for the first time that while overall IGT performance seems to be unimpaired in both ASD and OCD individuals, ASD boys show more nuanced differences on aspects of reward-based learning related to perseverative decision-making that may influence decisions at a finer level. This is in line with key cognitive and neurofunctional impairments in ASD that may be related to perseverative choice behaviour; for example, there is evidence for poor PFC-mediated cognitive flexibility in ASD (Geurts et al., 2004, Ozonoff et al., 2004, Verte et al., 2005, Sanders et al., 2008, Kriete and Noelle, 2015), which

seemingly fits with perseveration in stereotyped and repetitive behaviours observed clinically (American Psychiatric Association, 2013). In addition, inferior frontal and insular hyperactivation to reward extends the limited previous findings of reward processing in ASD, as it has been reported that adolescents with ASD have increased activation in the insula (Cascio et al., 2012a) as well as in left frontal regions (Schmitz et al., 2008) during reward receipt. It is also interesting to note that the location of activation in the present study was in anterior regions of the insula and largely extended into inferior frontal regions. The anterior insula has been implicated in ASD with regard to its involvement in interoception and salience processing (Uddin and Menon, 2009), although a meta-analysis found this region to be hypoactivated in ASD individuals. However, this meta-analysis included studies from a number of domains including social processing and theory of mind, possibly confounding these results. Therefore, the present finding of disorder-specific fronto-insular hyperactivation support these regions' unique implication in ASD but calls into question the specific role of this involvement such that fronto-insular regions may be differentially involved in social vs. non-social tasks of hot EF.

However, perhaps more striking is the fact that neurofunctional abnormalities during hot EF tasks were predominantly shared between ASD and OCD. During TD, ASD and OCD patients relative to control boys shared reduced activation to delayed versus immediate choices in right ventromedial and lateral OFC extending into medial and inferior PFC, and in lateral cerebellum, PCC, and precuneus. Both patient groups also shared reduced activation relative to controls to immediate versus delayed choices in ACC and vmPFC extending into left caudate and in bilateral inferior temporo-parietal regions. Moreover, on the IGT, ASD and OCD boys shared reduced activation relative to controls during decision-making in left DLPFC and right IFG and insula.

Both the TD task and the IGT require temporal foresight to make decisions that will be beneficial in the long term. Ventromedial and ventrolateral fronto-limbic regions are key areas for successful temporal foresight (Christakou et al., 2011, Peters and Büchel, 2011), and the mPFC is important for reward-based decision-making in healthy individuals (Remijnse et al., 2005, Finger et al., 2008, Euston et al., 2012). In ASD, these results support previous findings of ventromedial and fronto-limbic abnormalities during reward-based decision-making involving monetary reward (Schmitz et al., 2008, Dichter et al., 2012b, Dichter et al., 2012d, Kohls et al., 2013). The present study also extends these neurofunctional abnormalities to individuals with OCD, who have been shown to have both structural and functional deficits in orbitofronto-striatal networks (Menzies et al., 2008, Radua et al., 2010, Norman et al., 2016), including vmPFC, OFC and ACC projecting to striatal regions in adults and adolescents (Menzies et al., 2008, Brem et al., 2012). Moreover, these results are corroborated by findings of reduced DLPFC and caudate activation in adults with OCD relative to controls during planning and forward-thinking behaviour (van den Heuvel et al., 2005b, van den Heuvel et al., 2011). Collectively, this evidence of shared dysfunction in ventro-medial and dorsolateral prefronto-striatal regions between ASD and OCD boys suggests a common neurofunctional mechanism of hot EF dysfunction related to temporal foresight and forward planning. Moreover, shared reduced activation of PCC/precuneus/lateral cerebellum in both clinical groups compared to controls during choices of delayed reward is in line with similar evidence in ADHD individuals during TD (Rubia et al., 2009a), suggesting that reductions in this region may be a shared feature across a number of disorders which commonly emerge during childhood and exhibit features of impulsivity (Fineberg et al., 2009). Furthermore, enhanced activation in this region in both patient groups was related to improved task performance, suggesting a brain-

behaviour link related to impaired hot EF observable in adolescents with ASD and those with OCD.

In line with the DLPFC's role in working memory and value representation (Ridderinkhof et al., 2004, Li et al., 2010), as well as ventrolateral PFC and insular regions' roles in stimulus saliency and affective decision-making (Phillips et al., 2003), these results provide first evidence that adolescents with ASD and OCD may share deficits in their ability to assign emotional salience to decisions during hot EF, possibly indicating difficulty with goal-directed learning. This theory has been proposed in OCD (Gillan and Robbins, 2014), but these results suggest that this theory could be extended to ASD in the context of decision-making under ambiguity. Moreover, these results may suggest shared functional immaturity of decision-making networks incorporating these regions in ASD and OCD, as a previous study in healthy adolescents and adults found age-related changes within dorsal and ventrolateral PFC regions during the IGT (Christakou et al., 2013a). During the outcome anticipation phase of the IGT, both patient groups shared underactivation relative to controls in left orbitofrontal and ventrolateral PFC regions and the VS. Reduced activation in these regions during hot EF tasks of decision-making, particularly during reward anticipation and presentation but also during choice switching, has been well-documented in OCD (Remijnse et al., 2006, Chamberlain et al., 2008, Menzies et al., 2008, Britton et al., 2010, Figee et al., 2011, Jung et al., 2011). Moreover, fronto-striato-limbic abnormalities including reduced VS activation have been observed in ASD during outcome anticipation, presentation and reward learning (Dichter et al., 2012b, Kohls et al., 2013, D'Cruz et al., 2016). Therefore, these results collectively suggest that reduced ventrolateral prefrontal, orbitofrontal and ventral striatal activation during reward anticipation and receipt may be a shared neurofunctional abnormality common to individuals with ASD and OCD.

During the IGT, despite the fact that all three groups had comparable overall proportions of safe choices, computational modelling results showed shared differences in ASD and OCD boys compared to controls on two model parameters. Both ASD and OCD boys had lower average parameter estimates for choice consistency and reinforcement learning weight, suggesting that these groups shared differences in decision-making strategies that were distinct from the control group. This evidence is in line with previous findings that high-functioning ASD adolescents showed increased switching among deck choices on the IGT compared to controls (Johnson et al., 2006, Yechiam et al., 2010) and extends this evidence to OCD adolescents. In line with evidence of impaired reward learning in both groups on other reward-based decision-making hot EF tasks (Nielen et al., 2009, Scott-Van Zeeland et al., 2010b), both patient groups also showed less reliance of reinforcement learning strategies. Therefore, these collective results suggest that ASD and OCD boys exhibited increased exploratory behaviour independently of other choice parameters such as outcome sensitivity, presenting novel evidence for unique patterns of reward-based decision-making shared between ASD and OCD adolescents. Clinically, this shared decision-making style may relate to overlapping patterns of persistent repetitive behaviours.

In summary, these shared findings during hot EF tasks suggest dorsolateral and ventromedial prefronto-ventral striatal as well as temporo-parietal activation decreases in both disorders relative to controls, which may relate to abnormalities in hot EF and reward-based decision-making. Moreover, lateral cerebellar activation decreases were shared between ASD and OCD during TD, suggesting a shared mechanism for this cerebellar sub-region specific to hot EF abnormalities, in contrast to shared cerebellar vermis overactivation observed during sustained attention. Findings support evidence of temporo-parietal and cerebellar dysfunction commonly observed during social functions in ASD (Kana et al., 2014, Wang et al., 2014, Igelström et al., 2016) and extend this

evidence to OCD as a shared mechanism in the context of hot EF. Moreover, evidence of VS dysfunction during reward-related EF in both disorders is also supported (Dichter, 2012, Langen et al., 2012, Fineberg et al., 2014, Langen et al., 2014, Norman et al., 2016).

8.4 Conclusions

The findings from this thesis suggest that there are both shared and disorder-specific behavioural and neurobiological abnormalities in adolescent boys with ASD and with OCD compared to typically-developing control boys during tasks of cool and hot EF, as observed in a comparative meta-analysis and in experimental fMRI studies of sustained attention, temporal foresight and gambling. Structurally, children and adults with ASD and with OCD share reduced GMV relative to controls in medial prefrontal regions important for top-down control of ventromedial prefronto-striato-limbic systems of affect and motivation. These results were paralleled by the fMRI and conjunction meta-analyses which similarly showed shared overlapping functional reductions in this region. The reduced structure and function in MPFC were also observed in previous meta-analyses of other disorders such as anxiety, bipolar disorder, schizophrenia, depression and conduct disorder (Glahn et al., 2008, Goodkind et al., 2015, Alegria et al., 2016, Wise et al., 2016), many of which commonly develop in childhood/adolescence. However, disorder-specific increases in striato-insular GMV and activation during cognitive control were observed in OCD compared to ASD (and right striatal GMV was decreased in ASD), extending meta-analyses in OCD (Radua and Mataix-Cols, 2009, Radua et al., 2010). Recent mega-analyses suggest that these structural differences may be a developmental age-related effect, as striatal GMV abnormalities have been less consistently observed in children versus adults with OCD (Boedhoe et al., 2017) and are preserved across the lifespan in OCD compared to GMV

decline in healthy controls (deWit et al., 2014). ASD individuals had increased but OCD individuals had reduced GMV in left DLPFC, suggesting differential abnormalities that may relate to functions such as working memory and the link between prefrontal executive control regions and the BG (Petrides et al., 1993). These structural results were paralleled by fMRI results which showed reduced dorsolateral prefrontal activation specific to ASD, presumably related to poor frontal control over subcortical regions. Reduced DLPFC activation may also be a signature of specific impairments in attention-related aspects of cool EF tasks, as the DLPFC has been shown to be important for the representation and maintenance of attentional demands during EF (MacDonald et al., 2000). Interestingly, while DLPFC activation reductions were specific to ASD, reduced mPFC/ACC activation was observed as a shared deficit in both ASD and OCD. The aforementioned study from MacDonald and colleagues (MacDonald et al., 2000) also showed that the role of the DLPFC was distinct from that of the ACC, which was more closely linked to performance monitoring and evaluation during EF, suggesting dissociable roles for dorsal lateral versus medial prefrontal regions in the context of cognitive control that are, respectively, ASD-specific versus shared. These results collectively suggest that overall divergent structural and functional abnormalities in fronto-striatal networks including lateral prefrontal regions important for top-down control, as well as more bottom-up BG regions, may be identifying factors in the pathophysiology of these disorders.

In the fMRI meta-analysis of cognitive control studies, ASD also showed disorder-specific signatures of enhanced PCC activation, possibly related to reduced default-mode deactivation. Moreover, OCD individuals had disorder-specific decreased temporo-parietal activation, presumably reflecting deficits in posterior attention systems, whereas ASD-specific DLPFC abnormalities may be related to fronto-striatal attention network deficits (MacDonald et al., 2000).

Abnormalities during sustained attention were primarily disorder-specific to OCD relative to ASD, as OCD boys had decreased activation in left inferior-fronto-insular regions and right PCC and STL but progressively increased activation in rMPFC, important for attentional control. Shared increased activation relative to controls during sustained attention was observed in key cerebellar regions associated with sustained attention. During TD, behavioural deficits were disorder-specific to ASD boys indicating heightened impulsivity and lower tolerance for delays, but no robust disorder-specific neurofunctional effects were found on this task in either patient group. Indeed, predominantly shared abnormalities between ASD and OCD boys were observed during both hot EF tasks in fronto-striatal regions including ventromedial PFC and lateral OFC and caudate, as well as cerebellum, PCC and precuneus, and bilateral inferior temporo-parietal regions, suggesting shared deficits in the neural underpinnings of forward-thinking and motivated decision-making. Finally, during the IGT, both patient groups exhibited primarily shared abnormalities in decision-making strategies, showing less choice consistency and lower reliance on reinforcement learning, although ASD patients had disorder-specific abnormalities related to perseverative choice behaviour. Both groups shared reduced activation relative to controls in left dorsolateral prefrontal and right inferior and orbitofronto-insular regions key in reward-based decision-making and in left ventral fronto-striatal regions during outcome anticipation. However, during rewarded outcomes, ROI analyses showed that ASD boys had disorder-specific increased activation in left IFG and insula.

Overall, results suggest that both ASD and OCD share reductions in dmPFC/dACC during predominantly cool EF tasks, in this case sustained attention and cognitive control, presumably related to shared deficits in top-down control of vmPFC-limbic systems of affect and motivation. Conversely, dorsolateral, ventromedial and orbitofronto-striatal reductions were shared during hot EF tasks, suggesting common

mechanisms specifically in the context of emotionally-driven decision-making. These findings may relate clinically to symptoms related to reward saliency and problems with forward-thinking behaviour, although more studies are needed to formally test this relationship. Nonetheless, the identification of shared neurobiological mechanisms between ASD and OCD adolescents is an important step towards identifying and possibly treating abnormalities in trans-diagnostic behavioural phenotypes. Moreover, these studies provide first evidence to suggest that striato-insular and temporo-parietal abnormalities may be specific to OCD compared to ASD in the context of cool EF, but that similar abnormalities may be shared between these disorders in the context of hot EF. Furthermore, divergent shared findings in the cerebellum (shared increases during sustained attention, shared decreases during TD) were observed mostly in different cerebellar sub-regions (cerebellar vermis in SAT, lateral cerebellum in TD) and could also suggest a differential role for different parts of the cerebellum in the context of emotional (lateral) versus non-emotional (vermis) EF abnormalities common to ASD and OCD.

Given the subjective nature of current diagnostic tools to assess these disorders, there is much scope for the development of objective, biologically grounded markers with which to identify symptoms and target treatments that may be common or unique across these disorders. This is especially important in the case of ASD and OCD, two disorders that commonly develop at an early age and can have long-lasting, debilitating effects on an individual's life.

8.5 Strengths and limitations

These studies have a number of strengths but also some limitations which are discussed in this section.

One of the primary strengths of the fMRI studies conducted as part of this thesis is the investigation of mostly homogenous groups of patients; both the ASD and the OCD groups were all right-handed adolescent males between 11-17 years old who were free of psychiatric comorbidity and thoroughly assessed by consultant-level clinicians. Moreover, the majority of patients were medication naïve, with the exception of four OCD boys. It has been shown that handedness can have hemispheric effects in the brain (Knecht et al., 2000), so by including only right-handed boys, we were able to rule out any potential confounding effects handedness may have on brain activation (although this was not possible in the meta-analytic comparison). There is also evidence for sexual dimorphism in the brain (Sacher et al., 2013), particularly in individuals with ASD (Baron-Cohen et al., 2005). Therefore, recruiting only male participants increased sample homogeneity. Another strength of this study is the exclusion of psychiatric comorbidity from the clinical groups. It is known that ADHD, which is often comorbid with both ASD (van der Meer et al., 2012) and OCD (Brem et al., 2014), can have specific neurofunctional effects (Christakou et al., 2013b, Chantiluke et al., 2014b). Moreover, OCD-related disorders such as hoarding disorder and trichotillomania have been shown to be neurofunctionally distinct from OCD (Rauch et al., 2007, Tolin et al., 2014), so the exclusion of individuals with diagnoses of these related disorders was a particular strength, again adding to the homogeneity of the samples. Furthermore, the careful selection and detailed assessment of patients from National & Specialist paediatric clinics ensured that, through extensive interviews with highly trained consultant psychiatrists, the ASD group was not comorbid with OCD and that the OCD group was not comorbid with ASD, assurance that was further corroborated with well-validated and established parent rating questionnaires. Therefore, we could be fairly certain that any neurofunctional abnormalities observed in the study within each clinical group were specific to that disorder (although some caveats to this assertion are

discussed below). In addition, the inclusion of primarily medication-naïve adolescents was a study strength. ASD adolescents are occasionally prescribed psychotropic medication including SSRIs and antipsychotics (Benvenuto et al., 2013), and SSRIs are a common and often effective treatment in adolescent OCD (Soomro et al., 2008). It has been shown that these medications can have short (Carlisi et al., 2016a) and long-term neurostructural and neurofunctional effects (Navari and Dazzan, 2009, Murphy, 2010), so by investigating a primarily medication-naïve sample of ASD and OCD individuals, the potential confounding effects of medication use were removed, as findings remained largely unchanged when analyses were repeated excluding the four OCD patients who were prescribed medication. Moreover, it was not possible to include only medication-free individuals in the meta-analysis, but potential effects of SSRI use on meta-analytic findings were tested within the OCD group through meta-regression, and results showed that medication did not have a large effect on volumetric or activation differences, although insufficient information was provided to test similar associations among the ASD studies.

However, these studies are not without limitations. While group homogeneity is primarily a study strength, this somewhat reduces the generalisability and clinical applications of these findings, as it is uncommon in clinical practice to see such uniform groups of patients. Moreover, as mentioned throughout the experimental chapters of this thesis, although the absence of psychiatric comorbidity was confirmed by a consultant psychiatrist, the possibility that sub-threshold symptoms related to other disorders were present in our samples cannot be discounted, as it is relatively common for ASD and OCD individuals to exhibit symptoms related to other disorders without meeting criteria for a formal diagnosis of that disorder. Moreover, a limitation of this research is that specific measures assessing symptoms of anxiety and depression were not collected, and OCD or ASD were not formally excluded in the respective study groups via

structured interview specifically assessing these disorders. Future studies should quantitatively consider the possible impact these symptoms may have on neurocognitive differences across groups. Although there were no statistically significant differences in age among study groups, age is another factor that could potentially confound results, especially in the context of investigating developmental disorders. However, this was addressed by including age as a covariate in all fMRI analyses as well as in the confirmatory matched meta-analysis. Nonetheless, the fact that it was not possible due to available studies and low statistical power to conduct an age-stratified subgroup analysis for the meta-analysis is a limitation which highlights the need for more future work in child and adolescent populations.

Again, a study strength is the fact that the majority of participants were medication-naïve. However, due to practical restrictions and time constraints, it was necessary to include four adolescents with OCD who were prescribed stable does of SSRIs at the time of testing. However, the possible effects of medication were considered by either including medication status as a covariate in analyses or by repeating analyses excluding these four boys. Moreover, in the meta-analysis, medication use in OCD studies was considered in meta-regression analyses. All results largely showed that medication did not have a significant effect on brain function, but these sub-group results are somewhat difficult to interpret, as with only 16 patients in the OCD group, analyses were likely no longer adequately powered to detect differences.

8.6 Future work

Considering that this is the first set of studies to compare adolescents with ASD and with OCD on neuropsychological or neurofunctional measures, there is considerable scope for further research comparing the cognitive, structural and

functional substrates of these disorders, with wide-reaching clinical implications for diagnosis and treatment.

This thesis has provided novel evidence that executive function deficits commonly observed in ASD and OCD may be underpinned by both shared and disorder-specific brain mechanisms. Moreover, this work has produced evidence that performance on reward-based decision-making tasks such as the Iowa Gambling Task may be due to more nuanced individual differences in strategies employed to learn from feedback and implement decisions. These strategies include the degree to which an individual utilises reinforcement learning and the frequency with which an individual shifts between choices, behaviours which were abnormal in both ASD and OCD adolescents compared to controls. These findings present a convincing case that neurocomputational mechanisms are important to consider alongside neurofunctional differences when investigating the shared and disorder-specific neurobehavioral correlates that underpin psychiatric disorders. Moreover, based on constraints of the specific computational modelling tools used in this thesis, it was not possible to obtain individual parameter estimates for each subject. However, individual differences are an important consideration if we are to fully understand the mechanistic underpinnings of behaviour, and future studies should aim to investigate such differences.

The scope of this thesis limited investigation to three EF tasks. However, it is possible and indeed likely that abnormalities in regions observed in these investigations are also implicated in a number of other cognitive domains and tasks. Therefore, future studies should extend the present comparative results to other EF domains such as e.g. working memory and social motivation. In addition, it would be interesting in future fMRI studies to compare ASD with other disorders, including OCD, within the context of emotion processing to assess the degree to which neurofunctional abnormalities observed during these cognitive processes are truly disorder-specific and unique to

ASD. This research is important given the implication of social processing abnormalities among ASD adolescents (Baron-Cohen, 2001, Di Martino et al., 2009), the relative dearth of research into socio-emotional processes in other disorders such as OCD, and the co-morbidity of other emotion-related disorders such as anxiety in both ASD (Simonoff et al., 2008, Murphy et al., 2014) and OCD (Mataix-Cols et al., 2005). On the topic of comorbidity, future studies should also collect questionnaire measures probing behaviours related to other disorders including depression, anxiety and ADHD to more precisely quantify sub-threshold symptoms and how they may relate to observed abnormalities.

Based on the findings from these studies, one can begin to draw conclusions regarding the functional relationships among brain regions that were observed to be over or underactive relative to control groups. Therefore, functional connectivity analyses would be a logical next step for future studies. This is especially important given the hypotheses formulated relating to fronto-striatal circuitry and dysregulation within these and other (e.g. attention, salience, default-mode) networks. Given that the brain functions as an interconnected network of the regions, analyses investigating how these regions communicate with one another and how activity among these regions is correlated are necessary. This is an important next step in gaining a more complete understanding of functional mechanisms underpinning behaviour in ASD and OCD. Moreover, this information can inform clinically-relevant treatment development in the future, including identifying potential targets for neurostimulation and neurofeedback, cognitive bias modification, and psychopharmacological interventions.

Developmental effects on brain structure and function have been shown in studies across both ASD (Brambilla et al., 2003) and OCD (deWit et al., 2014). Therefore, it is important to, as this thesis has done, investigate brain abnormalities in younger age groups. However, it is essential that future studies broaden this approach

by investigating age-related changes across the lifespan of these disorders, including not only children and adolescents but also adults to study how the brain changes across the course of these disorders that often develop in childhood but persist into adulthood. Moreover, given that both ASD and OCD are associated with developmental changes across the lifespan (Courchesne, 2004, deWit et al., 2014), conducting longitudinal investigations of brain abnormalities is critical for a complete understanding of not only cross-sectional similarities and differences at different time points and developmental stages, but also a comparison of developmental trajectories over time between these disorders.

This is the first set of studies to compare individuals with non-comorbid ASD or OCD. It has provided evidence for shared and disorder-specific brain abnormalities between these disorders, but a critical next step is to compare these non-comorbid groups with a group of individuals with comorbid ASD and OCD. Other studies (e.g. (Chantiluke et al., 2014b)) have made this comparison with ADHD and autism and found that the comorbid ADHD/ASD group had brain abnormalities that were distinct from both non-comorbid patient groups, suggesting that comorbidity between these two disorders results in unique neural signatures that are not simply an additive pathology of the two conditions. To gain a complete understanding of the phenotypes that are indeed shared and disorder-specific to ASD and OCD, the comparison with a comorbid group of individuals is necessary.

A final limitation to consider is the issue of task-specificity. This thesis has focused on elucidating disorder-specificity of brain regions implicated in the pathophysiology of ASD and OCD during particular subdomains of executive functions, i.e. inhibitory control. This included tasks of motor and interference inhibition as well as switching. However, the specificity of brain abnormalities to each of the types of fMRI tasks employed has not been examined. Furthermore, it remains to be investigated

whether the two disorders share similar or different neurofunctional substrates in other task contexts such as emotion or social paradigms. It has been suggested that there may exist a generalised, non-specific task-independent brain network that is engaged during any task requiring higher-level cognitive resources, regardless of the cognitive construct being investigated (Hugdahl et al., 2015). Indeed, many of the brain regions observed in this thesis that were abnormally activated in patients relative to controls were partially overlapping among the three fMRI tasks, particularly in prefrontal and insular regions. Future studies should consider task-specificity of functional abnormalities and compare activation across more homogenous tasks or task domains as well as across groups. Such investigation would add to the literature of disorder-specificity introduced in this thesis by systematically examining whether certain domains of neurocognitive dysfunction are specific to one disorder or shared between the two.

8.7 Final remarks

In conclusion, this PhD has provided the first evidence of shared and disorder-specific brain abnormalities in boys with ASD compared to boys with OCD during sustained attention, temporal discounting, and the Iowa Gambling Task. Moreover, it has provided large-scale, meta-analytic evidence for shared and disorder-specific differences in brain structure and brain function during tasks of cognitive control in both children and adults with ASD or OCD. The main conclusions of this thesis can be summarised as follows:

1) In the multimodal comparative meta-analysis, children and adults with ASD and with OCD exhibited shared widespread reductions in both function and structure in mPFC and dACC. OCD individuals showed reduced temporo-parietal activation and enhanced structure and functional activation in BG and insula relative to controls and ASD individuals, who furthermore had reduced GMV in right-hemispheric BG

and insula as well as disorder-specific increased GMV but reduced function in DLPFC. These results suggest a disorder-dissociated difference in fronto-striatal executive networks resulting in poor top-down mediation during cognitive control. This is in line with theories of fronto-striatal dysregulation in OCD, with poor medial prefrontal control over enlarged and over-active striato-insular regions, but a general reduction in activation within dorsolateral and medial prefronto-striatal regions in ASD.

2) Boys with ASD had disorder-specific behavioural impairments on both hot EF tasks, as well as disorder-specific increased left IFG and insula activation to reward outcome during the IGT, suggesting an ASD-specific neurofunctional impairment in reward sensitivity. Boys with OCD had disorder-specific deficits only during sustained attention, where they had decreased activation in fronto-insular and temporo-parietal regions and increased activation in medial PFC compared to ASD and control boys. Although clinical utility of these findings is limited as yet, future research may extend this work into the identification of potentially useful biomarkers for differentiating between these two disorders.
3) Shared deficits were observed predominantly during hot EF tasks in ventromedial and lateral prefronto-striatal and inferior temporo-parietal regions during TD, in dorsolateral and inferior-fronto-insular as well as orbito-fronto-ventral striatal and lateral cerebellar regions during decision-making on the IGT, but also in the vermis of the cerebellum during sustained attention. Concurrent shared abnormalities in decision-making strategies were related to choice consistency and reinforcement learning. These results suggest that phenotypes of ventrolateral prefrontal and orbitofronto-ventral striato-insular and cerebellar dysfunction during hot EF may be common to ASD and OCD.

This study makes a novel contribution to the field, as it shows both shared and disorder-specific abnormalities in homogenous groups of boys with either ASD or OCD during three cognitive tasks. Most importantly, it provides the first direct comparison between these disorders on any measure of behaviour, cognitive function, or brain structure and function. Moreover, this approach provides important advances for the investigation of trans-diagnostic phenotypes, as outlined by recent efforts such as the Research Domain Criteria (RDoC; (Insel et al., 2010)). Although more research is needed to support these findings and inform any potential clinical and treatment implications, this thesis provides convincing evidence that there are shared and disorder-specific neurobiological factors that may be driving EF abnormalities and possibly respective as well as trans-diagnostic symptoms in each disorder, and that fMRI may be a useful tool for the further investigation of these factors.

APPENDIX A – PARTICIPANT RECRUITMENT AND QUESTIONNAIRE MEASURES

All study participants were adolescent boys between 11 and 17 years of age and were all right-handed, as first confirmed verbally by parents and later in writing with the Edinburgh Handedness Inventory (Oldfield, 1971), a ten-item questionnaire assessing whether participants perform various daily actions (e.g. writing, using a toothbrush) with the left or right hand.

Typically-developing control participants were recruited by local advertisement. Parents of all control participants completed a phone screen before being invited to the Institute of Psychiatry, Psychology and Neuroscience for study participation. Aside from basic information including contact details and date of birth, this phone screen asked questions to determine whether it was likely that the young person would meet inclusion criteria (and would not meet exclusion criteria) for study participation. Parents were asked whether their son was currently taking or had ever taken any psychiatric medication. It was specified by the researcher conducting the phone screen that this includes but is not limited to medication for ADHD such as stimulants, or for anxiety/depression or OCD such as SSRIs. Any other non-psychiatric medication use was also recorded and queried with a psychiatrist if the medication called into question study eligibility. Parents were also asked whether they had ever sought treatment or medical advice for their son related to psychiatric difficulties, mental health or neurological problems (and whether this resulted in any diagnosis), whether their son had ever experienced learning difficulties, and whether he had any history of substance use. Lastly, for MRI purposes, parents were asked whether their son was claustrophobic or had any metal in his mouth or body, such as dental work or surgical pins. If parents endorsed any of the above, follow-up questions were asked by the researcher to determine eligibility. Exclusion criteria for control participants were lifetime psychiatric

medication use, any psychiatric diagnosis, neurological abnormalities, learning disability, and MRI contraindications.

Boys with ASD and with OCD were recruited from Child and Adolescent Mental Health Services (CAMHS) within the South London and Maudsley (SLaM) NHS Trust. Boys with ASD were referred to services for assessment of ASD-related symptoms and behaviours, and autism was the primary clinical concern. ASD diagnosis was made using ICD-10 research criteria (WHO, 1992), and a consultant psychiatrist confirmed absence of any other psychiatric comorbidity based on observation. All ASD boys were medication naïve. To confirm ASD diagnosis, parents of ASD completed the Autism Diagnostic Interview – Revised (ADI-R; (Lord et al., 1994)), which is a semi-structured, clinician-administered interview for caregivers of individuals for whom ASD is a clinical concern or possible diagnosis. It consists of 93 items assessing three functional domains: language/communication, reciprocal social interaction and restricted, repetitive and stereotyped behaviours and interests. The interview procedure is highly structured and standardised, assessing five general content areas: background (education, previous diagnoses, medication history), communication (both early and current), social development and play (early and current), repetitive and restricted behaviours (current and lifetime), and general behaviour problems including aggression and self-injury. The interview usually lasts around 1½ hours, although for older children this estimate can be substantially longer. Items covered in the interview are scored by the rater on a scale of 0 ("*no definite behaviour of the type specified*") to 3 ("*extreme severity*"), though in scoring the items, scores of 3 get re-coded to 2 ("*definite abnormal behaviour*"). All items are scored for current behaviour unless the behaviour is relevant only to specific age periods. Scores are generated for each of the three domains: communication and language, social interaction and restricted, repetitive behaviours. ASD was classified if scores in all three domains exceeded specified cut-offs:

communication and language-8, social interaction-10 and restricted, repetitive behaviours-3. All ASD participants in this study scored above these cut-offs in all domains.

ASD boys also underwent the Autism Diagnostic Observation Schedule (ADOS; (Lord et al., 2000)). The ADOS is a semi-structured observational interview assessing communication, social interaction and imaginative play for individuals for whom ASD is a clinical concern or possible diagnosis. The ADOS consists of four modules based on varying levels of development and language abilities, and each module consists of standardised activities/tasks which allow the examiner to observe the presence or absence of behaviours associated with the ASD phenotype. Observation typically lasts around 45 minutes, and participants' responses during each activity are recorded. Within each module, the examiner deliberately varies his/her behaviour using a hierarchy of structured and unstructured social norms to 'press' the individual being observed to exhibit behaviours of relevance to the ASD phenotype. Overall ratings are made at the end of the schedule, where each item is scored on a three-point scale (0 – no evidence of abnormal behaviours related to autism to 3 – severe abnormalities). Scores are totalled into two domain scores: *communication* and *social interaction,* and one combined score: *communication and social interaction*. Autism and ASD diagnoses are then formulated through a diagnostic algorithm for each module. Cut-off scores for each domain for autism and ASD are as follows: *communication*: autism-4, ASD-2; *social interaction*: autism-7, ASD-4; *combined*: autism-12, ASD-7. All ASD participants scored about cut-offs for autism in all domains of the ADOS.

OCD participants were recruited mainly from the National & Specialist OCD clinic at the Michael Rutter Centre, SLaM NHS Foundation Trust. The remaining participants were recruited from other CAMHS services in the South London area. OCD diagnosis was made in accordance with ICD-10 research criteria (code F42) and

comorbidity with other psychiatric disorders was ruled out by a consultant psychiatrist. If expert clinical opinion called into question the possibility of comorbid symptoms or diagnosis, the individual was not included in the study. OCD diagnosis was confirmed with the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS; (Goodman et al., 1989)). Trained interviewers administered the CY-BOCS to the patient in the form of an extended semi-structured interview usually lasting upwards of two hours. The CY-BOCS divides symptoms into obsessions and compulsions and asks patients to endorse or deny specific behaviours associated with sub-domains within each category. Compulsions are divided into 9 domains: washing/cleaning, checking, repeating, ordering/arranging, counting, hoarding/saving, excessive games/superstitious behaviours, rituals involving other persons, and miscellaneous compulsions. Obsessions are divided into 8 domains: contamination, aggressive, sexual, hoarding/saving, magical thoughts/superstitions, somatic, religious, and miscellaneous. Scoring is completed at the end of each category (compulsions/obsessions) based on responses to 5 questions: time spent, interference, distress, resistance, and control. Responses are scored using a Likert scale of 0-4, where 0 indicates least severe and 4 indicates extremely severe. Responses to these 5 questions are totalled to obtain 2 sub-scores, *compulsions* and *obsessions*, and these sub-scores are added together to obtain the overall total score. Cut-offs for the total score are as follows: 0-7: subclinical, 8-15: mild, 16-23: moderate, 24-31: severe, 32-40: extreme. All OCD participants scored above the cut-off for moderate severity. All OCD participants were medication naïve with the exception of 4 boys who were prescribed stable doses of SSRIs at the time of testing.

Parents of ASD individuals and typically-developing controls completed the Social Communication Questionnaire (SCQ; (Rutter et al., 2003)) – current version. The SCQ is a brief 40 item screening measure for ASD consisting of yes/no questions. Each response which endorses symptoms potentially related to ASD receives a score of 1,

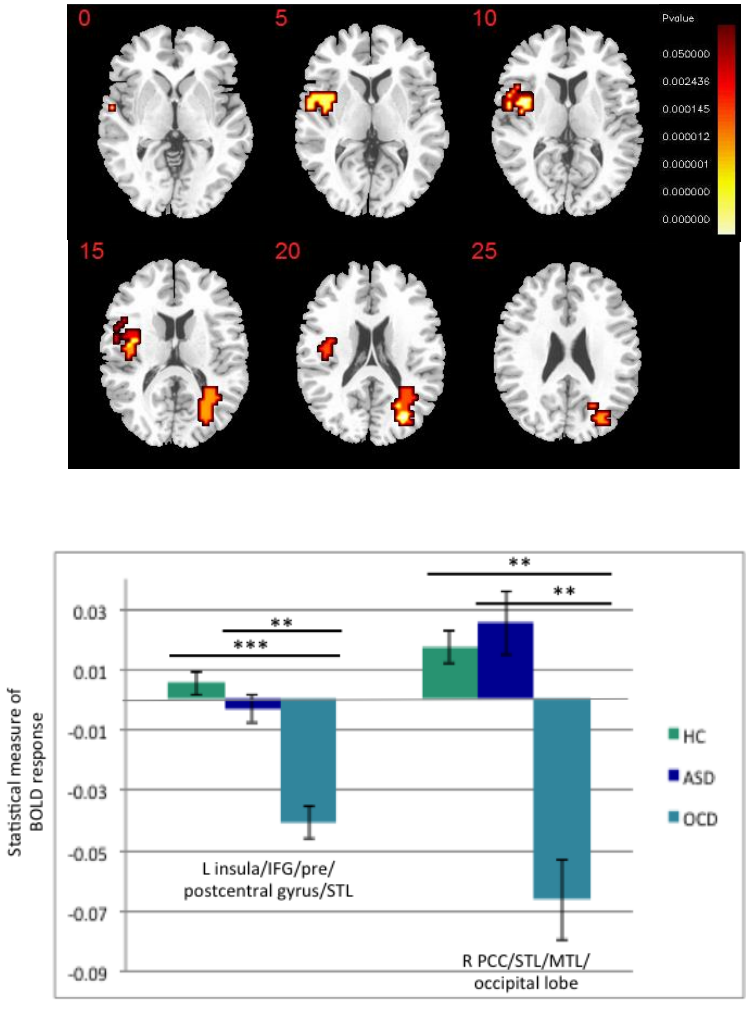
while negative responses receive a score of 0. Responses are summed to obtain a total score. Cut-off score for ASD symptoms that would likely result in a diagnosis is 15, though individuals who score in the 10-15 range are often referred for further evaluation. Due to the fact that some of the OCD participants were recruited prior to the timeline of this thesis, SCQ scores were not available for the entire OCD sample and were thus not reported in the empirical chapters of this thesis, but all OCD participants who did complete the SCQ scored below cut-off for ASD.

Parents of all participants also completed the Strengths and Difficulties Questionnaire (SDQ; (Goodman and Scott, 1999)). The SDQ is a parent-rated brief 25 item behavioural screening questionnaire for children and adolescents probing behaviours over the last six months. The 25 questions ask about positive and negative attributes divided into 5 sub-domains: emotional, conduct, hyperactivity/inattention, peer relationships, and prosocial behaviour. Responses are made by indicating for each item *Not True*, *Somewhat True*, or *Certainly True*. Based on whether the question is asking about positive or negative behaviour, responses are given a score of 0, 1 or 2, where 0 indicates no problems, and 2 indicates clear presence of problems. The scores from these domains are added together to obtain sub-scores, and the first 4 domains are added together to obtain a *total difficulties* score. The SDQ also includes an impact supplement, which contains additional questions about whether the respondent thinks the young person has a problem and probes chronicity, distress, social impairment and burden to others. Responses on this supplement contribute to a separate impact score and do not influence total score. Sub-scores as well as total difficulties scores can be categorised into broad cut-offs according to ‘normal’, ‘borderline’ and ‘abnormal’ ranges. These cut-offs for total difficulties are, normal: 0-13, borderline: 14-16, abnormal: 17-40.

MRI suitability of clinical participants was confirmed with parents at the time of clinical assessment if the child was otherwise deemed suitable for study participation based on clinician confirmation of diagnosis (based on ICD-10 research criteria) and absence of any psychiatric comorbidity including depression and ADHD in all participants, ASD in OCD patients and controls, and OCD in ASD individuals and controls.

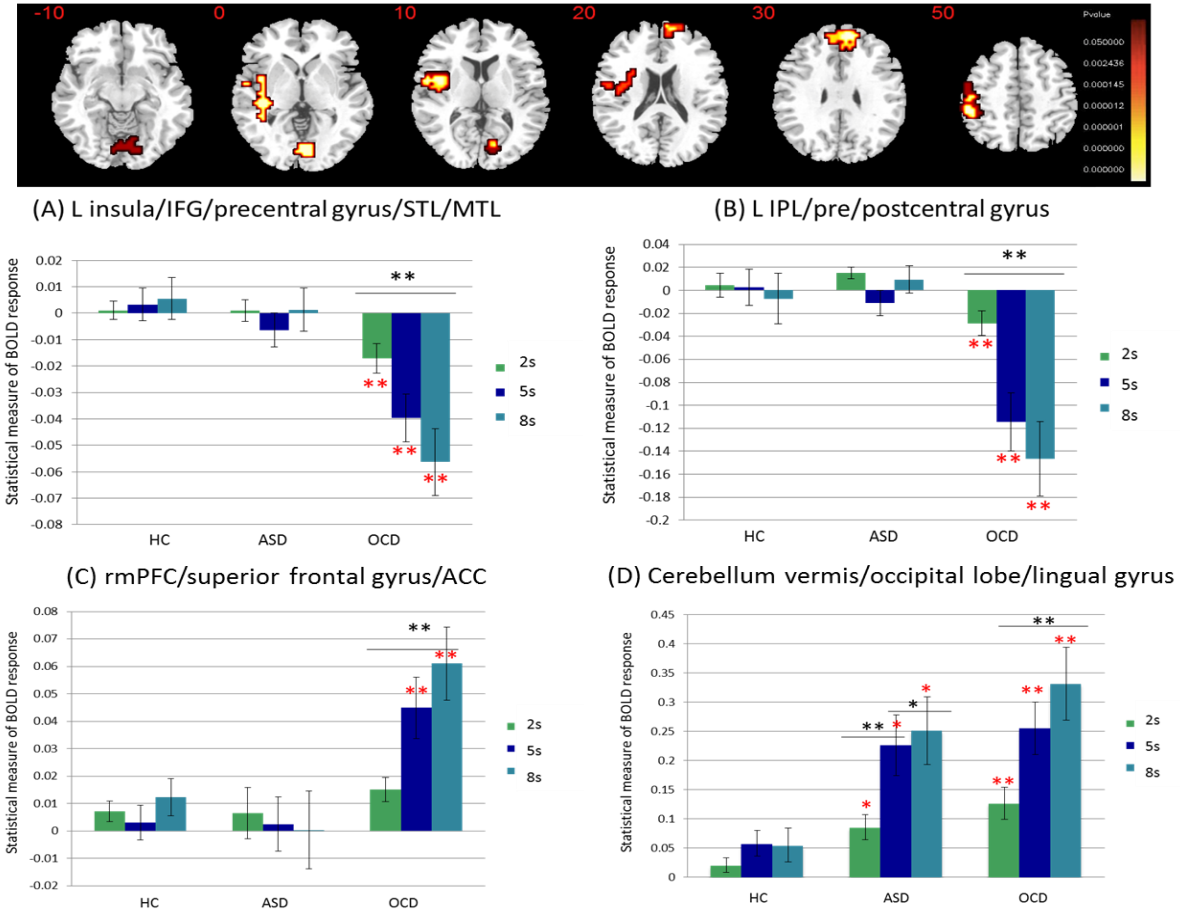
APPENDIX B – BRAIN ACTIVATION SSQ PLOTS WITH STANDARD ERROR BARS

Sustained Attention Task (Chapter 5)



Appendix B, Figure 1 - Between-group differences in brain activation between healthy control boys, boys with Autism Spectrum Disorder (ASD) and boys with Obsessive-Compulsive Disorder (OCD)

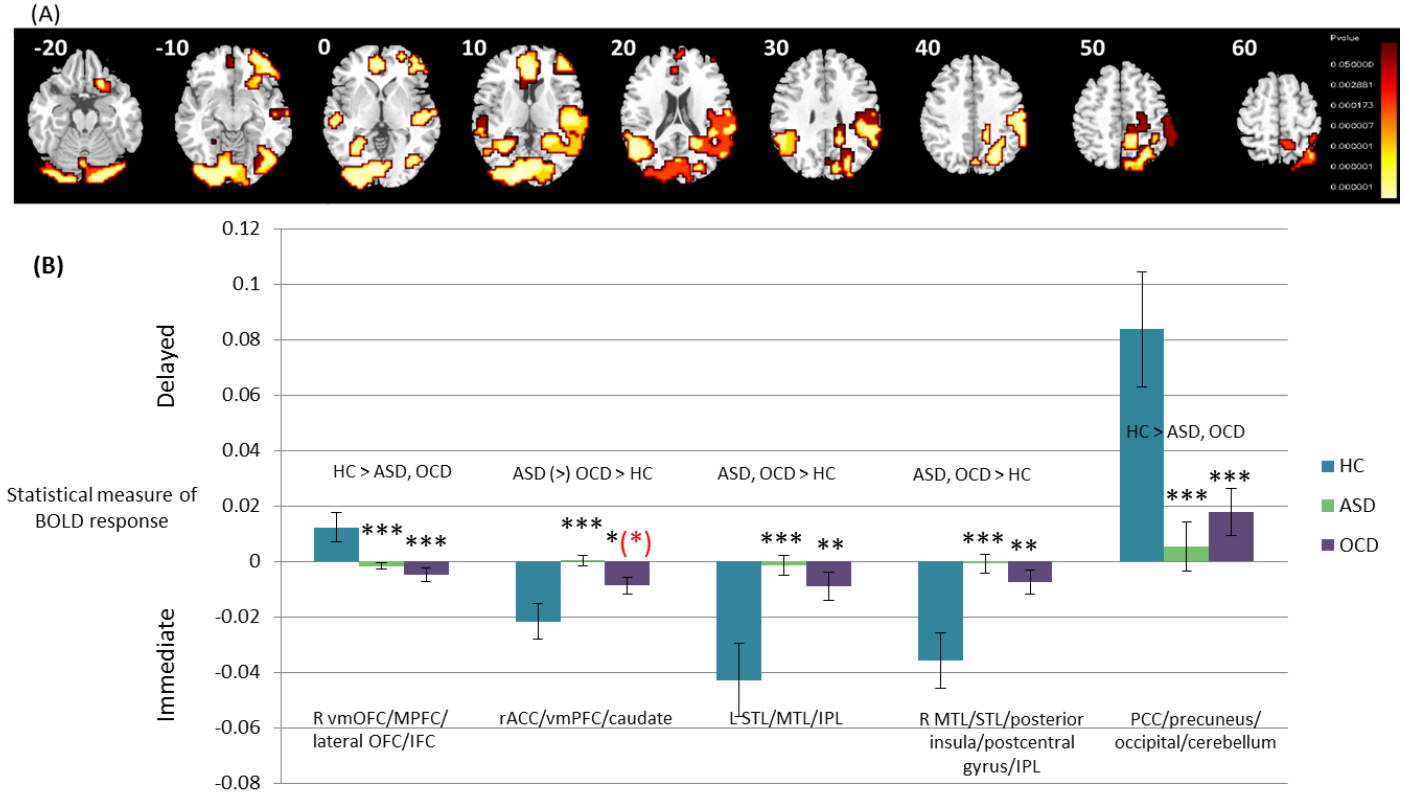
Analysis of variance (ANOVA) showing the main effect of group on brain activation for all delays (2s, 5s, 8s) combined, contrasted against 0.5s trials. Talairach z-coordinates are shown for slice distance (in mm) from the intercommissural line. The right side corresponds with the right side of the brain. **indicates significant at $p<0.005$, ***indicates significant at $p<0.001$



Appendix B, Figure 2 – Group x Delay interaction between healthy control boys, boys with Autism Spectrum Disorder (ASD) and boys with Obsessive-Compulsive Disorder (OCD) and delay condition (2s, 5s, 8s)

Analysis of variance (ANOVA) showing group-by-delay interaction effects on brain activation. Talairach z-coordinates are shown for slice distance (in mm) from the intercommissural line. The right side corresponds with the right side of the brain. Red asterisks indicate significant difference between diagnostic group and controls. Black asterisks indicate significant difference within group between conditions. *indicates significance at $p<0.05$, **indicates significance at $p<0.005$.

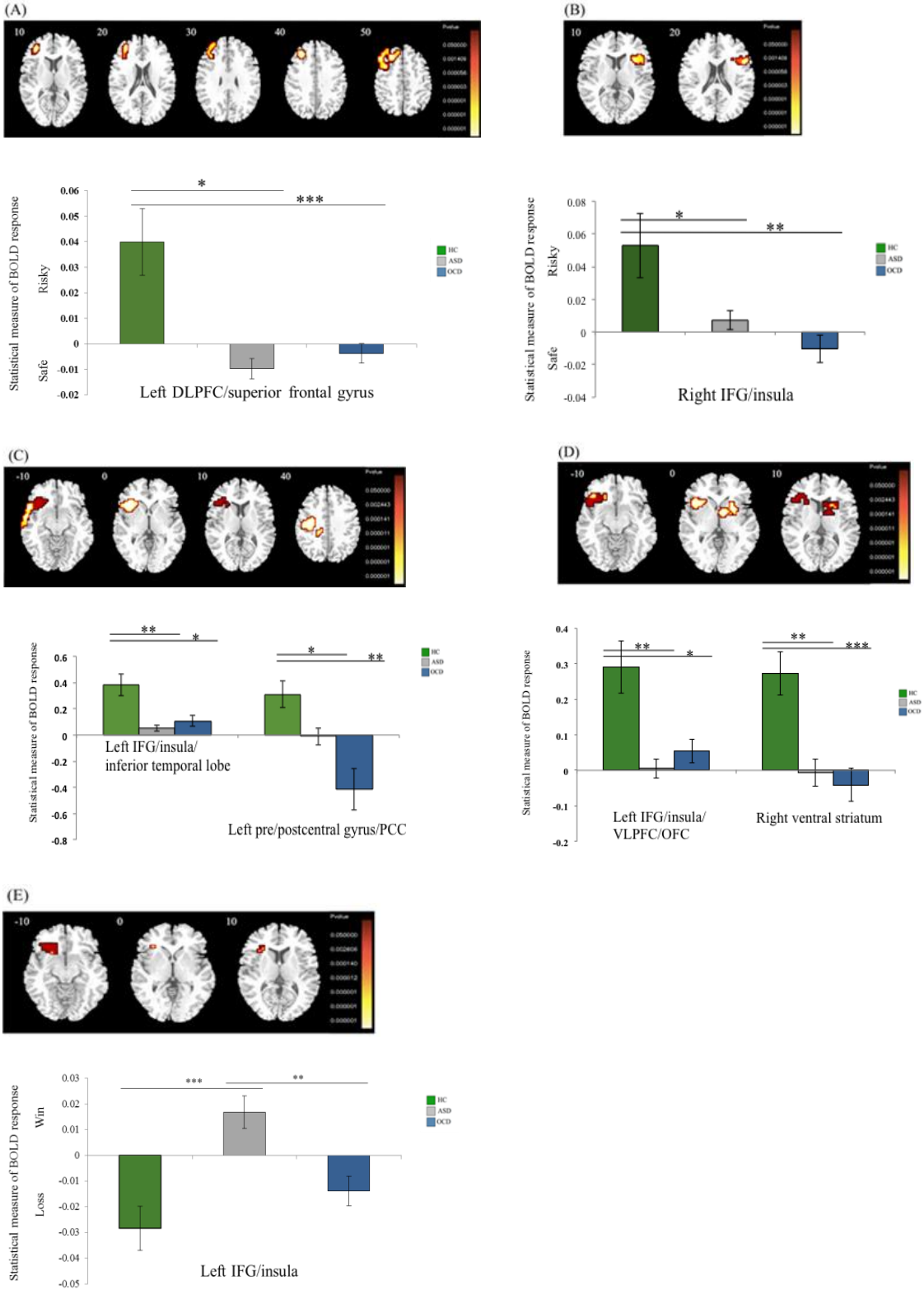
Temporal Discounting Task (Chapter 6)



Appendix B, Figure 3 – Between-group activation differences for delayed minus immediate choices

(A) Axial slices showing split-plot analysis of variance (ANOVA) effects of group on brain activation to delayed – immediate choices. Talairach *Z* coordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the image corresponds to the right side of the brain.
(B) Extracted statistical measures of BOLD response are shown for each of the three groups for each of the brain regions that showed a significant group effect. **Black** asterisks indicate a significant difference between controls and patient group. **Red** asterisk indicates a difference between the two patient groups. (*)= significant at a trend level; *=significant at the $p<.05$ level; **=significant at the $p\leq.005$ level; ***=significant at the $p\leq.001$ level.
Abbreviations: ASD, autism spectrum disorder; BOLD, blood oxygen level dependent; HC, healthy controls; IFC, inferior frontal cortex; IPL, inferior parietal lobe; LOFC, lateral orbitofrontal cortex; L, left; MPFC, medial prefrontal cortex; MTL, middle temporal lobe; OCD, obsessive-compulsive disorder; PCC, posterior cingulate cortex; R, right; rACC, rostral anterior cingulate cortex; STL, superior temporal lobe; vmOFC, ventromedial orbitofrontal cortex

Iowa Gambling Task (Chapter 7)



Appendix B, Figure 4 – Between-group differences in brain activation between healthy control boys, boys with autism spectrum disorder (ASD) and boys with obsessive-compulsive disorder (OCD)

Analysis of variance (ANOVA) showing the main effect of group on brain activation for the three phases of the Iowa Gambling Task. (A) Whole-brain results of the group effect during decision-making (choice phase, safe vs. risky), (B) Region of interest (ROI) results of the group effect during decision-making (choice phase, safe vs. risky), (C) Whole-brain results of the group effect during outcome anticipation,

(D) ROI results of the group effect during outcome anticipation, (E) ROI results of the group effect during outcome presentation (win vs. loss). Talairach z-coordinates are shown for slice distance (in mm) from the intercommissural line. The right side of the image corresponds with the right side of the brain. * indicates significance at the $p<0.05$ level, ** indicates significance at the $p<0.01$ level, *** indicates significance at the $p<0.001$ level.

APPENDIX C – COMPARISON OF CORRELATIONS BETWEEN BRAIN ACTIVATION AND TASK PERFORMANCE

Chapters 6 and 7 of this thesis report correlations between SSQs extracted from brain regions which significantly differed in activation between groups and task performance measures. This appendix outlines a formal comparison of these correlations between groups using Fisher's *r*-to-*z* transformation.

Temporal discounting (Chapter 6)

Chapter 6 reports that there was a significant correlation between AUC, the performance measure for the TD task, and cerebellum/occipital lobe/PCC/precuneus activation in ASD (r=-0.66, p<0.001) and OCD (r=-0.45, p<0.05) individuals. These correlations were statistically different between controls (r=-0.25, p=0.28) and ASD boys (z=1.69, p<0.05) but not ASD and OCD boys (z=0.97, p=0.17) or OCD boys and controls (z=-0.66, p=0.26).

AUC was also associated with activation in L STL/IPL in the ASD group (r=0.41, p=0.03). This correlation did not statistically differ from that in the control group (r=0.14, p=0.55; z=-0.94, p=0.17) or the OCD group (r=0.35, p=0.13; z=-0.22, p=0.41), and correlations in the OCD group and control group did not significantly differ (z=0.66, p=0.26).

Lastly on the TD task, AUC was associated with activation in right MTL/STL/insula in the ASD (r=0.39, p=0.04) and OCD (r=0.59, p=0.006) groups. These correlations did not significantly differ between controls (r=0.32, p=0.16) and ASD individuals (z=-0.231, p=0.409) or OCD individuals (z=-1.02, p=0.16) nor between ASD and OCD individuals (z=-0.89, p=0.19).

Iowa Gambling Task (Chapter 7)

On the IGT, advantageous preference ratio was associated with left DLPFC activation during whole brain analysis of the choice phase in the control group (r=0.43, p=0.008). This correlation was significantly different from that in the OCD group (r=-.28, p=0.09; z=0.01, p=0.03) but did not statistically differ from that in the ASD group (r=0.03, p=0.84; z=1.33, p=0.18). Correlations in the ASD and OCD groups did not differ from one another (z=0.96, p=0.34).

Advantageous preference ratio was also associated with left IFG/insula activation during the whole brain analysis of the anticipation phase in controls (r=0.45, p=0.005). However, this correlation did not statistically differ from that in ASD (r=0.17, p=0.25; z=0.16, p=0.33) or OCD individuals (r=0.18, p=0.27; z=0.19, p=0.37). Moreover, correlations in the ASD and OCD groups did not significantly differ (z=-0.04, p=0.97).

REFERENCES

ABELL, F., KRAMS, M., ASHBURNER, J., PASSINGHAM, R., FRISTON, K., FRACKOWIAK, R., HAPPÉ, F., FRITH, C. & FRITH, U. (1999). The neuroanatomy of autism: a voxel- based whole brain analysis of structural scans. *Neuroreport*. 10(8): 1647-1651.

ABRAMOVITCH, A., ABRAMOWITZ, J. S. & MITTELMAN, A. (2013). The neuropsychology of adult obsessive–compulsive disorder: A meta-analysis. *Clinical Psychology Review*. 33(8): 1163-1171.

ABRAMOVITCH, A., ABRAMOWITZ, J. S., MITTELMAN, A., STARK, A., RAMSEY, K. & GELLER, D. A. (2015a). Research Review: Neuropsychological test performance in pediatric obsessive–compulsive disorder – a meta-analysis. *Journal of Child Psychology and Psychiatry*. 56(8): 837-847.

ABRAMOVITCH, A., DAR, R., MITTELMAN, A. & WILHELM, S. (2015b). Comorbidity Between Attention Deficit/Hyperactivity Disorder and Obsessive-Compulsive Disorder Across the Lifespan: A Systematic and Critical Review. *Harvard Review of Psychiatry*. 23(4): 245-262.

ABRAMOWITZ, J. S., DEACON, B. J., OLATUNJI, B. O., WHEATON, M. G., BERMAN, N. C., LOSARDO, D., TIMPANO, K. R., MCGRATH, P. B., RIEMANN, B. C. & ADAMS, T. (2010). Assessment of obsessive-compulsive symptom dimensions: Development and evaluation of the Dimensional Obsessive-Compulsive Scale. *Psychological assessment*. 22(1): 180.

ACHENBACH, T. M. (1991). *Manual for the Child Behavior Checklist/4-18 and 1991 profile*. Department of Psychiatry, University of Vermont Burlington, VT.

ACOSTA, M. T. & PEARL, P. L. (2004). Imaging data in autism: from structure to malfunction. *Seminars in Pediatric Neurology*. 11(3): 205-213.

ADAMS, N. C. & JARROLD, C. (2009). Inhibition and the validity of the Stroop task for children with autism. *Journal of Autism and Developmental Disorders*. 39(8): 1112-1121.

ADOLPHS, R. (2001). The neurobiology of social cognition. *Current Opinion in Neurobiology*. 11(2): 231-239.

AGAM, Y., JOSEPH, R. M., BARTON, J. J. S. & MANOACH, D. S. (2010). Reduced cognitive control of response inhibition by the anterior cingulate cortex in autism spectrum disorders. *NeuroImage*. 52(1): 336-347.

AHMED, F., RAS, J. & SEEDAT, S. (2012). Volumetric structural magnetic resonance imaging findings in pediatric posttraumatic stress disorder and obsessive-compulsive disorder: a systematic review. *Frontiers in Psychology*. 3(568).

AHN, W.-Y., HAINES, N. & ZHANG, L. (2016). Revealing neuro-computational mechanisms of reinforcement learning and decision-making with the hBayesDM package. *bioRxiv*.

AHN, W.-Y., KRAWITZ, A., KIM, W., BUSEMEYER, J. R. & BROWN, J. W. (2011). A model-based fMRI analysis with hierarchical Bayesian parameter estimation. *Journal of Neuroscience, Psychology, and Economics*. 4(2): 95.

AHN, W.-Y., VASILEV, G., LEE, S.-H., BUSEMEYER, J. R., KRUSCHKE, J. K., BECHARA, A. & VASSILEVA, J. (2014). Decision-making in stimulant and opiate addicts in protracted abstinence: evidence from computational modeling with pure users. *Frontiers in Psychology*. 5(849).

AIGNER, M., SACHS, G., BRUCKMÜLLER, E., WINKLBAUR, B., ZITTERL, W., KRYSPIN-EXNER, I., GUR, R. & KATSCHNIG, H. (2007). Cognitive and

emotion recognition deficits in obsessive–compulsive disorder. *Psychiatry Research*. 149(1): 121-128.

ALBIN, R. L., YOUNG, A. B. & PENNEY, J. B. (1989). The functional anatomy of basal ganglia disorders. *Trends in neurosciences*. 12(10): 366-375.

ALEGRIA, A. A., RADUA, J. & RUBIA, K. (2016). Meta-Analysis of fMRI Studies of Disruptive Behavior Disorders. *American Journal of Psychiatry*. 173(11): 1119-1130.

ALEXANDER, G. E. & CRUTCHER, M. D. (1990). Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends in neurosciences*. 13(7): 266-271.

ALEXANDER, G. E., DELONG, M. R. & STRICK, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neuroscience*. 9(1): 357-381.

ALLEN, G., BUXTON, R. B., WONG, E. C. & COURCHESNE, E. (1997). Attentional activation of the cerebellum independent of motor involvement. *Science*. 275(5308): 1940-1943.

ALLEN, G. & COURCHESNE, E. (2001). Attention function and dysfunction in autism. *Frontiers in bioscience: a journal and virtual library*. 6D105-119.

ALLEN, G. & COURCHESNE, E. (2003). Differential effects of developmental cerebellar abnormality on cognitive and motor functions in the cerebellum: an fMRI study of autism. *American Journal of Psychiatry*. 160(2): 262-273.

ALONSO, P., ORBEGOZO, A., PUJOL, J., LÓPEZ-SOLÀ, C., FULLANA, M. À., SEGALÀS, C., REAL, E., SUBIRÀ, M., MARTÍNEZ-ZALACAÍN, I., MENCHÓN, J. M., HARRISON, B. J., CARDONER, N. & SORIANO-MAS, C. (2013). Neural correlates of obsessive–compulsive related dysfunctional

beliefs. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 4725-32.

ALVARENGA, P. G., DO ROSÁRIO, M. C., BATISTUZZO, M. C., DINIZ, J. B., SHAVITT, R. G., DURAN, F. L., DOUGHERTY, D. D., BRESSAN, R. A., MIGUEL, E. C. & HOEXTER, M. Q. (2012). Obsessive-compulsive symptom dimensions correlate to specific gray matter volumes in treatment-naïve patients. *Journal of Psychiatric Research*. 46(12): 1635-1642.

AMARAL, D. G., SCHUMANN, C. M. & NORDAHL, C. W. (2008). Neuroanatomy of autism. *Trends in neurosciences*. 31(3): 137-145.

AMBROSE, J. (1973). Computerized transverse axial scanning (tomography): Part 2. Clinical application*. *The British journal of radiology*. 46(552): 1023-1047.

AMBROSINO, S., BOS, D., VAN RAALTEN, T., KOBUSSEN, N., VAN BELLE, J., ORANJE, B. & DURSTON, S. (2014). Functional connectivity during cognitive control in children with autism spectrum disorder: an independent component analysis. *Journal of Neural Transmission*. 121(9): 1145-1155.

AMERICAN PSYCHIATRIC ASSOCIATION (2013). *Diagnostic and statistical manual of mental disorders, 5th edition*. 5th. American Psychiatric Publishing: Arlington, VA.

ANHOLT, G., CATH, D., OPPEN, P., EIKELENBOOM, M., SMIT, J., MEGEN, H. & BALKOM, A. L. M. (2010). Autism and ADHD Symptoms in Patients with OCD: Are They Associated with Specific OC Symptom Dimensions or OC Symptom Severity? *Journal of Autism and Developmental Disorders*. 40(5): 580-589.

ANTROP, I., STOCK, P., VERTÉ, S., WIERSEMA, J. R., BAEYENS, D. & ROEYERS, H. (2006). ADHD and delay aversion: the influence of non-

temporal stimulation on choice for delayed rewards. *Journal of Child Psychology and Psychiatry*. 47(11): 1152-1158.

AOUIZERATE, B., GUEHL, D., CUNY, E., ROUGIER, A., BIOULAC, B., TIGNOL, J. & BURBAUD, P. (2004). Pathophysiology of obsessive–compulsive disorder: a necessary link between phenomenology, neuropsychology, imagery and physiology. *Progress in Neurobiology*. 72(3): 195-221.

ARMSTRONG, T., ZALD, D. H. & OLATUNJI, B. O. (2011). Attentional control in OCD and GAD: Specificity and associations with core cognitive symptoms. *Behav Res Ther*. 49(11): 756-762.

ARON, A. R. (2011). From reactive to proactive and selective control: developing a richer model for stopping inappropriate responses. *Biological Psychiatry*. 69(12): e55-e68.

ARONOWITZ, B. R., HOLLANDER, E., DECARIA, C., COHEN, L., SAOUD, J. B., STEIN, D., LIEBOWITZ, M. R. & ROSEN, W. G. (1994). Neuropsychology of obsessive compulsive disorder: preliminary findings. *Cognitive and Behavioral Neurology*. 7(2): 81-86.

ATMACA, M., YILDIRIM, H., OZDEMIR, H., TEZCAN, E. & KURSAD POYRAZ, A. (2007). Volumetric MRI study of key brain regions implicated in obsessive–compulsive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 31(1): 46-52.

ATMACA, M., YILDIRIMB, H., OZDEMIRB, H., AYDINB, A., TEZCANA, E. & OZLERA, S. (2006). Volumetric MRI assessment of brain regions in patients with refractory obsessive–compulsive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 30(6): 1051-1057.

AYLWARD, E. H., MINSHEW, N. J., FIELD, K., SPARKS, B. F. & SINGH, N. (2002). Effects of age on brain volume and head circumference in autism. *Neurology*. 59(2): 175-183.

BAIRD, G., SIMONOFF, E., PICKLES, A., CHANDLER, S., LOUCAS, T., MELDRUM, D. & CHARMAN, T. (2006). Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP). *The Lancet*. 368(9531): 210-215.

BANICH, M. T. (2004). *Cognitive neuroscience and neuropsychology*. Houghton Mifflin College Division.

BANKS, G. P., MIKELL, C. B., YOUNGERMAN, B. E. & ET AL. (2015). Neuroanatomical characteristics associated with response to dorsal anterior cingulotomy for obsessive-compulsive disorder. *JAMA Psychiatry*. 72(2): 127-135.

BANNON, S., GONSALVEZ, C. J., CROFT, R. J. & BOYCE, P. M. (2002). Response inhibition deficits in obsessive–compulsive disorder. *Psychiatry Research*. 110(2): 165-174.

BARI, A. & ROBBINS, T. W. (2013). Inhibition and impulsivity: Behavioral and neural basis of response control. *Progress in Neurobiology*. 108(0): 44-79.

BARON-COHEN, S. (2001). Theory of mind and autism: A review. In *International review of research in mental retardation: Autism (vol. 23)*, pp. 169-184. Academic Press: San Diego, CA, US.

BARON-COHEN, S. (2002). The extreme male brain theory of autism. *Trends in Cognitive Sciences*. 6(6): 248-254.

BARON-COHEN, S. & HAMMER, J. (1997). Is autism an extreme form of the" male brain"? *Advances in Infancy research*. 11193-218.

BARON-COHEN, S., KNICKMEYER, R. C. & BELMONTE, M. K. (2005). Sex differences in the brain: implications for explaining autism. *Science*. 310(5749): 819-823.

BARON-COHEN, S., LESLIE, A. M. & FRITH, U. (1985). Does the autistic child have a "theory of mind" ? *Cognition*. 21(1): 37-46.

BARON-COHEN, S., LOMBARDO, M. V., AUYEUNG, B., ASHWIN, E., CHAKRABARTI, B. & KNICKMEYER, R. (2011). Why are autism spectrum conditions more prevalent in males? *PLoS Biol*. 9(6): e1001081.

BARON-COHEN, S., RING, H. A., BULLMORE, E. T., WHEELWRIGHT, S., ASHWIN, C. & WILLIAMS, S. (2000). The amygdala theory of autism. *Neuroscience & Biobehavioral Reviews*. 24(3): 355-364.

BAXTER JR, L., SAXENA, S., BRODY, A., ACKERMANN, R., COLGAN, M., SCHWARTZ, J., ALLEN-MARTINEZ, Z., FUSTER, J. & PHELPS, M. (1996). Brain mediation of obsessive-compulsive disorder symptoms: evidence from functional brain imaging studies in the human and nonhuman primate. In *Seminars in Clinical Neuropsychiatry*, pp. 32-47.

BAXTER, L. (1999). Functional imaging of brain systems mediating obsessive-compulsive disorder. *Neurobiology of Mental Illness. Oxford University Press, New York*. 534-547.

BAXTER, L., CLARK, E., IQBAL, M. & ACKERMANN, R. (2001). Cortical/subcortical systems in the mediation of obsessive-compulsive disorder: modeling the brain's mediation of a classic 'neurosis'. *Frontal-subcortical circuits in psychiatric and neurological disorders*. 207-230.

BAXTER, L. R., PHELPS, M. E., MAZZIOTTA, J. C., GUZE, B. H., SCHWARTZ, J. M. & SELIN, C. E. (1987). Local cerebral glucose metabolic rates in obsessive-

compulsive disorder: a comparison with rates in unipolar depression and in normal controls. *Archives of General Psychiatry*. 44(3): 211-218.

BECHARA, A., DAMASIO, A. R., DAMASIO, H. & ANDERSON, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition*. 50(1–3): 7-15.

BECHARA, A., DAMASIO, H., TRANEL, D. & DAMASIO, A. R. (1997). Deciding Advantageously Before Knowing the Advantageous Strategy. *Science*. 275(5304): 1293-1295.

BELMONTE, M. K. & YURGELUN-TODD, D. A. (2003). Functional anatomy of impaired selective attention and compensatory processing in autism. *Cognitive Brain Research*. 17(3): 651-664.

BENATTI, B., DELL'OSSO, B., ARICI, C., HOLLANDER, E. & ALTAMURA, A. C. (2014). Characterizing impulsivity profile in patients with obsessive–compulsive disorder. *International Journal of Psychiatry in Clinical Practice*. 18(3): 156-160.

BENEDETTI, F., POLETTI, S., RADAELLI, D., POZZI, E., GIACOSA, C., RUFFINI, C., FALINI, A. & SMERALDI, E. (2012). Caudate gray matter volume in obsessive-compulsive disorder is influenced by adverse childhood experiences and ongoing drug treatment. *Journal of clinical psychopharmacology*. 32(4): 544-547.

BENNETTO, L., PENNINGTON, B. F. & ROGERS, S. J. (1996). Intact and impaired memory functions in autism. *Child Development*. 67(4): 1816-1835.

BENVENUTO, A., BATTAN, B., PORFIRIO, M. C. & CURATOLO, P. (2013). Pharmacotherapy of autism spectrum disorders. *Brain and Development*. 35(2): 119-127.

BENZINA, N., MALLET, L., BURGUIÈRE, E., N'DIAYE, K. & PELISSOLO, A. (2016). Cognitive Dysfunction in Obsessive-Compulsive Disorder. *Current Psychiatry Reports*. 18(9): 1-11.

BERLIN, H. A., SCHULZ, K. P., ZHANG, S., TURETZKY, R., ROSENTHAL, D. & GOODMAN, W. (2015). Neural correlates of emotional response inhibition in obsessive-compulsive disorder: A preliminary study. *Psychiatry Research: Neuroimaging*. 234(2): 259-264.

BERSANI, G., QUARTINI, A., RATTI, F., PAGLIUCA, G. & GALLO, A. (2013). Olfactory identification deficits and associated response inhibition in obsessive-compulsive disorder: On the scent of the orbitofronto–striatal model. *Psychiatry Research*. 210(1): 208-214.

BICKEL, W. K., PITCOCK, J. A., YI, R. & ANGTUACO, E. J. C. (2009). Congruence of BOLD Response across Intertemporal Choice Conditions: Fictive and Real Money Gains and Losses. *The Journal of Neuroscience*. 29(27): 8839-8846.

BISHOP, D. V. M. & NORBURY, C. F. (2005). Executive functions in children with communication impairments, in relation to autistic symptomatology: 2: Response inhibition. *Autism*. 9(1): 29-43.

BLAIR, R., COLLEDGE, E. & MITCHELL, D. (2001). Somatic markers and response reversal: is there orbitofrontal cortex dysfunction in boys with psychopathic tendencies? *Journal of abnormal child psychology*. 29(6): 499-511.

BLAKEMORE, S.-J. (2008). The social brain in adolescence. *Nat Rev Neurosci*. 9(4): 267-277.

BLAKEMORE, S.-J. & SIRIGU, A. (2003). Action prediction in the cerebellum and in the parietal lobe. *Experimental Brain Research*. 153(2): 239-245.

BLAKEMORE, S. J. & CHOUDHURY, S. (2006). Development of the adolescent brain: implications for executive function and social cognition. *Journal of Child Psychology and Psychiatry*. 47(3- 4): 296-312.

BLUMBERG, S. J., BRAMLETT, M. D., KOGAN, M. D., SCHIEVE, L. A., JONES, J. R. & LU, M. C. (2013). Changes in prevalence of parent-reported autism spectrum disorder in school-aged US children: 2007 to 2011–2012. *National health statistics reports*. 65(20): 1-7.

BODDAERT, N., CHABANE, N., GERVAIS, H., GOOD, C., BOURGEOIS, M., PLUMET, M., BARTHELEMY, C., MOUREN, M., ARTIGES, E. & SAMSON, Y. (2004). Superior temporal sulcus anatomical abnormalities in childhood autism: a voxel-based morphometry MRI study. *NeuroImage*. 23(1): 364-369.

BOEDHOE, P. S. W., SCHMAAL, L., ABE, Y., AMEIS, S. H., ARNOLD, P. D., BATISTUZZO, M. C., BENEDETTI, F., BEUCKE, J. C., BOLLETTINI, I., BOSE, A., BREM, S., CALVO, A., CHENG, Y., CHO, K. I. K., DALLASPEZIA, S., DENYS, D., FITZGERALD, K. D., FOUCHE, J.-P., GIMÉNEZ, M., GRUNER, P., HANNA, G. L., HIBAR, D. P., HOEXTER, M. Q., HU, H., HUYSER, C., IKARI, K., JAHANSHAD, N., KATHMANN, N., KAUFMANN, C., KOCH, K., KWON, J. S., LAZARO, L., LIU, Y., LOCHNER, C., MARSH, R., MARTÍNEZ-ZALACAÍN, I., MATAIX-COLS, D., MENCHÓN, J. M., MINUZZI, L., NAKAMAE, T., NAKAO, T., NARAYANASWAMY, J. C., PIRAS, F., PIRAS, F., PITTENGER, C., REDDY, Y. C. J., SATO, J. R., SIMPSON, H. B., SORENI, N., SORIANO-MAS, C., SPALLETTA, G., STEVENS, M. C., SZESZKO, P. R., TOLIN, D. F., VENKATASUBRAMANIAN, G., WALITZA, S., WANG, Z., VAN WINGEN, G. A., XU, J., XU, X., YUN, J.-Y., ZHAO, Q., ENIGMA OCD

WORKING GROUP, THOMPSON, P. M., STEIN, D. J., VAN DEN HEUVEL, O. A. & GROUP, T. M. O. T. E. O. W. (2017). Distinct Subcortical Volume Alterations in Pediatric and Adult OCD: A Worldwide Meta- and Mega-Analysis. *American Journal of Psychiatry*. 174(1): 60-69.

BOISSEAU, C. L., THOMPSON-BRENNER, H., CALDWELL-HARRIS, C., PRATT, E., FARCHIONE, T. & BARLOW, D. H. (2012). Behavioral and cognitive impulsivity in obsessive–compulsive disorder and eating disorders. *Psychiatry Research*. 200(2): 1062-1066.

BONDE, E. (2000). Comorbidity and subgroups in childhood autism. *European Child & Adolescent Psychiatry*. 9(1): 7-10.

BONILHA, L., CENDES, F., RORDEN, C., ECKERT, M., DALGALARRONDO, P., LI, L. M. & STEINER, C. E. (2008). Gray and white matter imbalance – Typical structural abnormality underlying classic autism? *Brain and Development*. 30(6): 396-401.

BOOTH, R. & HAPPÉ, F. (2010). "Hunting with a knife and … fork": Examining central coherence in autism, attention deficit/hyperactivity disorder, and typical development with a linguistic task. *Journal of Experimental Child Psychology*. 107(4-5): 377-393.

BOULTER, C., FREESTON, M., SOUTH, M. & RODGERS, J. (2014). Intolerance of uncertainty as a framework for understanding anxiety in children and adolescents with autism spectrum disorders. *Journal of Autism and Developmental Disorders*. 44(6): 1391-1402.

BRAMBILLA, P., HARDAN, A., DI NEMI, S. U., PEREZ, J., SOARES, J. C. & BARALE, F. (2003). Brain anatomy and development in autism: review of structural MRI studies. *Brain Research Bulletin*. 61(6): 557-569.

BRAMMER, M. J., BULLMORE, E. T., SIMMONS, A., WILLIAMS, S. C. R., GRASBY, P. M., HOWARD, R. J., WOODRUFF, P. W. R. & RABE-HESKETH, S. (1997). Generic brain activation mapping in functional magnetic resonance imaging: A nonparametric approach. *Magnetic Resonance Imaging*. 15(7): 763-770.

BRECKEL, T. P., GIESSING, C. & THIEL, C. M. (2011). Impact of brain networks involved in vigilance on processing irrelevant visual motion. *NeuroImage*. 55(4): 1754-1762.

BREITER, H. C., AHARON, I., KAHNEMAN, D., DALE, A. & SHIZGAL, P. (2001). Functional imaging of neural responses to expectancy and experience of monetary gains and losses. *Neuron*. 30(2): 619-639.

BREITER, H. C., RAUCH, S. L., KWONG, K. K., BAKER, J. R., WEISSKOFF, R. M., KENNEDY, D. N., KENDRICK, A. D., DAVIS, T. L., JIANG, A. & COHEN, M. S. (1996). Functional magnetic resonance imaging of symptom provocation in obsessive-compulsive disorder. *Archives of General Psychiatry*. 53(7): 595.

BREM, S., GRÜNBLATT, E., DRECHSLER, R., RIEDERER, P. & WALITZA, S. (2014). The neurobiological link between OCD and ADHD. *Attention Deficit and Hyperactivity Disorders*. 6(3): 175-202.

BREM, S., HAUSER, T. U., IANNACCONE, R., BRANDEIS, D., DRECHSLER, R. & WALITZA, S. (2012). Neuroimaging of cognitive brain function in paediatric obsessive compulsive disorder: a review of literature and preliminary meta-analysis. *Journal of Neural Transmission*. 119(11): 1425-1448.

BRENNAN, B. P., TKACHENKO, O., SCHWAB, Z. J., JUELICH, R. J., RYAN, E. M., ATHEY, A. J., POPE, H. G., JENIKE, M. A., BAKER, J. T., KILLGORE, W. D. S., HUDSON, J. I., JENSEN, J. E. & RAUCH, S. L. (2015). An

Examination of Rostral Anterior Cingulate Cortex Function and Neurochemistry in Obsessive-Compulsive Disorder. *Neuropsychopharmacology*. 40(8): 1866-1876.

BRIEBER, S., NEUFANG, S., BRUNING, N., KAMP- BECKER, I., REMSCHMIDT, H., HERPERTZ- DAHLMANN, B., FINK, G. R. & KONRAD, K. (2007). Structural brain abnormalities in adolescents with autism spectrum disorder and patients with attention deficit/hyperactivity disorder. *Journal of Child Psychology and Psychiatry*. 48(12): 1251-1258.

BRITTON, J. C., RAUCH, S. L., ROSSO, I. M., KILLGORE, W. D. S., PRICE, L. M., RAGAN, J., CHOSAK, A., HEZEL, D. M., PINE, D. S., LEIBENLUFT, E., PAULS, D. L., JENIKE, M. A. & STEWART, S. E. (2010). Cognitive Inflexibility and Frontal-Cortical Activation in Pediatric Obsessive-Compulsive Disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 49(9): 944-953.

BROOKS, S. J., NAIDOO, V., ROOS, A., FOUCHÉ, J.-P., LOCHNER, C. & STEIN, D. J. (2015). Early-life adversity and orbitofrontal and cerebellar volumes in adults with obsessive–compulsive disorder: voxel-based morphometry study. *The British Journal of Psychiatry*.

BROTHERS, L. (2002). The social brain: a project for integrating primate behavior and neurophysiology in a new domain. *Foundations in social neuroscience*. 367-385.

BRUGHA, T. S., MCMANUS, S., BANKART, J., SCOTT, F., PURDON, S., SMITH, J., BEBBINGTON, P., JENKINS, R. & MELTZER, H. (2011). Epidemiology of autism spectrum disorders in adults in the community in England. *Archives of General Psychiatry*. 68(5): 459-465.

BRUN, C. C., NICOLSON, R., LEPORÉ, N., CHOU, Y. Y., VIDAL, C. N., DEVITO, T. J., DROST, D. J., WILLIAMSON, P. C., RAJAKUMAR, N. & TOGA, A. W. (2009). Mapping brain abnormalities in boys with autism. *Human Brain Mapping*. 30(12): 3887-3900.

BRUNSDON, V. E. A., COLVERT, E., AMES, C., GARNETT, T., GILLAN, N., HALLETT, V., LIETZ, S., WOODHOUSE, E., BOLTON, P. & HAPPÉ, F. (2015). Exploring the cognitive features in children with autism spectrum disorder, their co-twins, and typically developing children within a population-based sample. *Journal of Child Psychology and Psychiatry*. 56(8): 893-902.

BUHLE, J. T., SILVERS, J. A., WAGER, T. D., LOPEZ, R., ONYEMEKWU, C., KOBER, H., WEBER, J. & OCHSNER, K. N. (2014). Cognitive reappraisal of emotion: a meta-analysis of human neuroimaging studies. *Cerebral Cortex*. 24(11): 2981-2990.

BULLMORE, E., BRAMMER, M., RABE-HESKETH, S., CURTIS, V., MORRIS, R., WILLIAMS, S., SHARMA, T. & MCGUIRE, P. (1999a). Methods for diagnosis and treatment of stimulus-correlated motion in generic brain activation studies using fMRI. *Human Brain Mapping*. 7(1): 38-48.

BULLMORE, E., LONG, C., SUCKLING, J., FADILI, J., CALVERT, G., ZELAYA, F., CARPENTER, T. A. & BRAMMER, M. (2001). Colored noise and computational inference in neurophysiological (fMRI) time series analysis: resampling methods in time and wavelet domains. *Human Brain Mapping*. 12(2): 61-78.

BULLMORE, E. T., SUCKLING, J., OVERMEYER, S., RABE-HESKETH, S., TAYLOR, E. & BRAMMER, M. J. (1999b). Global, voxel, and cluster tests, by theory and permutation, for a difference between two groups of structural MR

images of the brain. *Medical Imaging, IEEE Transactions on Medical Imaging*. 18(1): 32-42.

BUSH, G., LUU, P. & POSNER, M. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci*. 4215 - 222.

CADMAN, T., SPAIN, D., JOHNSTON, P., RUSSELL, A., MATAIX-COLS, D., CRAIG, M., DEELEY, Q., ROBERTSON, D., MURPHY, C., GILLAN, N., WILSON, C. E., MENDEZ, M., ECKER, C., DALY, E., FINDON, J., GLASER, K., CONSORTIUM, M. A., HAPPÉ, F. & MURPHY, D. (2015). Obsessive-Compulsive Disorder in Adults with High-Functioning Autism Spectrum Disorder: What Does Self-Report with the OCI-R Tell Us? *Autism Research*. 8(5): 477-485.

CAI, W., RYALI, S., CHEN, T., LI, C.-S. R. & MENON, V. (2014). Dissociable Roles of Right Inferior Frontal Cortex and Anterior Insula in Inhibitory Control: Evidence from Intrinsic and Task-Related Functional Parcellation, Connectivity, and Response Profile Analyses across Multiple Datasets. *The Journal of Neuroscience*. 34(44): 14652-14667.

CALDERONI, S., RETICO, A., BIAGI, L., TANCREDI, R., MURATORI, F. & TOSETTI, M. (2012). Female children with autism spectrum disorder: an insight from mass-univariate and pattern classification analyses. *NeuroImage*. 59(2): 1013-1022.

CARDINAL, R. N. (2006). Neural systems implicated in delayed and probabilistic reinforcement. *Neural Networks*. 19(8): 1277-1301.

CARLISI, C. O., CHANTILUKE, K., NORMAN, L., CHRISTAKOU, A., BARRETT, N., GIAMPIETRO, V., BRAMMER, M., SIMMONS, A. & RUBIA, K. (2016a). The effects of acute fluoxetine administration on temporal discounting in youth with ADHD. *Psychological Medicine*. 46(06): 1197-1209.

CARLISI, C. O., NORMAN, L. J., LUKITO, S. S., RADUA, J., MATAIX-COLS, D. & RUBIA, K. (2016b). Comparative Multimodal Meta-analysis of Structural and Functional Brain Abnormalities in Autism Spectrum Disorder and Obsessive-Compulsive Disorder. *Biological Psychiatry*.

CARMIN, C. N., WIEGARTZ, P. S., YUNUS, U. & GILLOCK, K. L. (2002). Treatment of late- onset OCD following basal ganglia infarct. *Depression and Anxiety*. 15(2): 87-90.

CARMONA, S., BASSAS, N., ROVIRA, M., GISPERT, J.-D., SOLIVA, J.-C., PRADO, M., TOMAS, J., BULBENA, A. & VILARROYA, O. (2007). Pediatric OCD structural brain deficits in conflict monitoring circuits: A voxel-based morphometry study. *Neuroscience Letters*. 421(3): 218-223.

CARPENTER, B., GELMAN, A., HOFFMAN, M., LEE, D., GOODRICH, B., BETANCOURT, M., BRUBAKER, M. A., GUO, J., LI, P. & RIDDELL, A. (2016). Stan: A probabilistic programming language. *J Stat Softw*.

CARPER, R. A. & COURCHESNE, E. (2000). Inverse correlation between frontal lobe and cerebellum sizes in children with autism. *Brain*. 123(4): 836-844.

CARPER, R. A. & COURCHESNE, E. (2005). Localized enlargement of the frontal cortex in early autism. *Biological Psychiatry*. 57(2): 126-133.

CASCIO, C. J., FOSS-FEIG, J. H., HEACOCK, J. L., NEWSOM, C. R., COWAN, R. L., BENNINGFIELD, M. M., ROGERS, B. P. & CAO, A. (2012a). Response of neural reward regions to food cues in autism spectrum disorders. *Journal of Neurodevelopmental Disorders*. 4(1): 9.

CASCIO, C. J., FOSS-FEIG, J. H., HEACOCK, J. L., NEWSOM, C. R., COWAN, R. L., BENNINGFIELD, M. M., ROGERS, B. P. & CAO, A. (2012b). Response of neural reward regions to food cues in autism spectrum disorders. *Journal of Neurodevelopmental Disorders*. 4(1): 1.

CASEY, B., JONES, R. M. & HARE, T. A. (2008). The adolescent brain. *Annals of the New York Academy of Sciences*. 1124(1): 111-126.

CASEY, B. J. & JONES, R. M. (2010). Neurobiology of the Adolescent Brain and Behavior: Implications for Substance Use Disorders. *Journal of the American Academy of Child & Adolescent Psychiatry*. 49(12): 1189-1201.

CASTELLI, F., FRITH, C., HAPPÉ, F. & FRITH, U. (2002). Autism, Asperger syndrome and brain mechanisms for the attribution of mental states to animated shapes. *Brain*. 125(8): 1839-1849.

CAUDA, F., GEDA, E., SACCO, K., D'AGATA, F., DUCA, S., GEMINIANI, G. & KELLER, R. (2011). Grey matter abnormality in autism spectrum disorder: an activation likelihood estimation meta-analysis study. *Journal of Neurology, Neurosurgery & Psychiatry*. 82(12): 1304-1313.

CAVALLARO, R., CAVEDINI, P., MISTRETTA, P., BASSI, T., ANGELONE, S. M., UBBIALI, A. & BELLODI, L. (2003). Basal-corticofrontal circuits in schizophrenia and obsessive-compulsive disorder: a controlled, double dissociation study. *Biological Psychiatry*. 54(4): 437-443.

CAVEDINI, P., GORINI, A. & BELLODI, L. (2006). Understanding obsessive–compulsive disorder: focus on decision making. *Neuropsychology review*. 16(1): 3-15.

CAVEDINI, P., RIBOLDI, G., D'ANNUCCI, A., BELOTTI, P., CISIMA, M. & BELLODI, L. (2002). Decision-making heterogeneity in obsessive-compulsive disorder: ventromedial prefrontal cortex function predicts different treatment outcomes. *Neuropsychologia*. 40(2): 205-211.

CAVEDINI, P., ZORZI, C., PICCINNI, M., CAVALLINI, M. C. & BELLODI, L. (2010). Executive Dysfunctions in Obsessive-Compulsive Patients and

Unaffected Relatives: Searching for a New Intermediate Phenotype. *Biological Psychiatry*. 67(12): 1178-1184.

CHACKO, R. C., CORBIN, M. A. & HARPER, R. G. (2000). Acquired obsessive-compulsive disorder associated with basal ganglia lesions. *The Journal of neuropsychiatry and clinical neurosciences*. 12(2): 269-272.

CHAMBERLAIN, S., BLACKWELL, A., FINEBERG, N. A., ROBBINS, T. & SAHAKIAN, B. (2005). The neuropsychology of obsessive compulsive disorder: the importance of failures in cognitive and behavioural inhibition as candidate endophenotypic markers. *Neuroscience & Biobehavioral Reviews*. 29(3): 399-419.

CHAMBERLAIN, S., MENZIES, L., HAMPSHIRE, A., SUCKLING, J., FINEBERG, N., DEL CAMPO, N., AITKEN, M., CRAIG, K., OWEN, A. M., BULLMORE, E. T., ROBBINS, T. W. & SAHAKIAN, B. J. (2008). Orbitofrontal Dysfunction in Patients with Obsessive-Compulsive Disorder and Their Unaffected Relatives. *Science*. 321(5887): 421-422.

CHAMBERLAIN, S. R., FINEBERG, N. A., BLACKWELL, A. D., CLARK, L., ROBBINS, T. W. & SAHAKIAN, B. J. (2007a). A neuropsychological comparison of obsessive–compulsive disorder and trichotillomania. *Neuropsychologia*. 45(4): 654-662.

CHAMBERLAIN, S. R., FINEBERG, N. A., BLACKWELL, A. D., ROBBINS, T. W. & SAHAKIAN, B. J. (2006). Motor Inhibition and Cognitive Flexibility in Obsessive-Compulsive Disorder and Trichotillomania. *American Journal of Psychiatry*. 163(7): 1282-1284.

CHAMBERLAIN, S. R., FINEBERG, N. A., MENZIES, L. A., BLACKWELL, A. D., BULLMORE, E. T., CHIR, B., ROBBINS, T. W. & SAHAKIAN, B. J. (2007b). Impaired cognitive flexibility and motor inhibition in unaffected first-degree

relatives of patients with obsessive-compulsive disorder. *American Journal of Psychiatry*.

CHANTILUKE, K., BARRETT, N., GIAMPIETRO, V., BRAMMER, M., SIMMONS, A., MURPHY, D. G. & RUBIA, K. (2015a). Inverse Effect of Fluoxetine on Medial Prefrontal Cortex Activation During Reward Reversal in ADHD and Autism. *Cerebral Cortex*. 25(7): 1757-1770.

CHANTILUKE, K., BARRETT, N., GIAMPIETRO, V., BRAMMER, M., SIMMONS, A. & RUBIA, K. (2014a). Disorder-dissociated effects of fluoxetine on brain function of working memory in attention deficit hyperactivity disorder and autism spectrum disorder. *Psychological Medicine*. 451195-1205.

CHANTILUKE, K., BARRETT, N., GIAMPIETRO, V., SANTOSH, P., BRAMMER, M., SIMMONS, A., MURPHY, D. & RUBIA, K. (2015b). Inverse fluoxetine effects on inhibitory brain activation in non-comorbid boys with ADHD and with ASD. *Psychopharmacology*. 232(12): 2071-2082.

CHANTILUKE, K., CHRISTAKOU, A., MURPHY, C. M., GIAMPIETRO, V., DALY, E. M., BRAMMER, M., MURPHY, D. G. & RUBIA, K. (2014b). Disorder-specific functional abnormalities during temporal discounting in youth with Attention Deficit Hyperactivity Disorder (ADHD), Autism and comorbid ADHD and Autism. *Psychiatry Research: Neuroimaging*. 223113-120.

CHEN, J., SILK, T., SEAL, M., DALLY, K. & VANCE, A. (2013). Widespread decreased grey and white matter in paediatric obsessive-compulsive disorder (OCD): A voxel-based morphometric MRI study. *Psychiatry Research: Neuroimaging*. 213(1): 11-17.

CHEN, S., CHIEN, Y., WU, C., SHANG, C., WU, Y. & GAU, S. (2016). Deficits in executive functions among youths with autism spectrum disorders: an age-stratified analysis. *Psychological Medicine*. 46(8): 1625-1638.

CHENG, B., HUANG, X., LI, S., HU, X., LUO, Y., WANG, X., YANG, X., QIU, C., YANG, Y., ZHANG, W., BI, F., ROBERTS, N. & GONG, Q. (2015). Gray Matter Alterations in Post-Traumatic Stress Disorder, Obsessive–Compulsive Disorder, and Social Anxiety Disorder. *Frontiers in Behavioral Neuroscience*. 9219.

CHEVALLIER, C., KOHLS, G., TROIANI, V., BRODKIN, E. S. & SCHULTZ, R. T. (2012). The social motivation theory of autism. *Trends in Cognitive Sciences*. 16(4): 231-239.

CHIEN, Y.-L., GAU, S. S.-F., SHANG, C.-Y., CHIU, Y.-N., TSAI, W.-C. & WU, Y.-Y. (2015). Visual memory and sustained attention impairment in youths with autism spectrum disorders. *Psychological Medicine*. 45(11): 2263-2273.

CHMIELEWSKI, W. X. & BESTE, C. (2015). Action control processes in autism spectrum disorder – Insights from a neurobiological and neuroanatomical perspective. *Progress in Neurobiology*. 12449-83.

CHOI, J.-S., KANG, D.-H., KIM, J.-J., HA, T.-H., LEE, J.-M., YOUN, T., KIM, I. Y., KIM, S. I. & KWON, J. S. (2004). Left anterior subregion of orbitofrontal cortex volume reduction and impaired organizational strategies in obsessive-compulsive disorder. *Journal of Psychiatric Research*. 38(2): 193-199.

CHOI, J.-S., SHIN, Y.-C., JUNG, W. H., JANG, J. H., KANG, D.-H., CHOI, C.-H., CHOI, S.-W., LEE, J.-Y., HWANG, J. Y. & KWON, J. S. (2012). Altered Brain Activity during Reward Anticipation in Pathological Gambling and Obsessive-Compulsive Disorder. *PLoS ONE*. 7(9): e45938.

CHRIST, S. E., HOLT, D. D., WHITE, D. A. & GREEN, L. (2007). Inhibitory control in children with autism spectrum disorder. *Journal of Autism and Developmental Disorders*. 37(6): 1155-1165.

CHRIST, S. E., KESTER, L. E., BODNER, K. E. & MILES, J. H. (2011). Evidence for selective inhibitory impairment in individuals with autism spectrum disorder. *Neuropsychology*. 25(6): 690.

CHRISTAKOU, A., BRAMMER, M., GIAMPIETRO, V. & RUBIA, K. (2009a). Right Ventromedial and Dorsolateral Prefrontal Cortices Mediate Adaptive Decisions under Ambiguity by Integrating Choice Utility and Outcome Evaluation. *The Journal of Neuroscience*. 29(35): 11020-11028.

CHRISTAKOU, A., BRAMMER, M. & RUBIA, K. (2011). Maturation of limbic corticostriatal activation and connectivity associated with developmental changes in temporal discounting. *NeuroImage*. 54(2): 1344-1354.

CHRISTAKOU, A., GERSHMAN, S. J., NIV, Y., SIMMONS, A., BRAMMER, M. & RUBIA, K. (2013a). Neural and psychological maturation of decision-making in adolescence and young adulthood. *Journal of Cognitive Neuroscience*. 25(11): 1807-1823.

CHRISTAKOU, A., HALARI, R., SMITH, A. B., IFKOVITS, E., BRAMMER, M. & RUBIA, K. (2009b). Sex-dependent age modulation of frontostriatal and temporo-parietal activation during cognitive control. *NeuroImage*. 48(1): 223-236.

CHRISTAKOU, A., MURPHY, C., CHANTILUKE, K., CUBILLO, A., SMITH, A., GIAMPIETRO, V., DALY, E., ECKER, C., ROBERTSON, D. & MURPHY, D. (2013b). Disorder-specific functional abnormalities during sustained attention in youth with Attention Deficit Hyperactivity Disorder (ADHD) and with Autism. *Molecular psychiatry*. 18(2): 236-244.

CHRISTIAN, C. J., LENCZ, T., ROBINSON, D. G., BURDICK, K. E., ASHTARI, M., MALHOTRA, A. K., BETENSKY, J. D. & SZESZKO, P. R. (2008). Gray matter structural alterations in obsessive–compulsive disorder: Relationship to

neuropsychological functions. *Psychiatry Research: Neuroimaging*. 164(2): 123-131.

COLDREN, J. T. & HALLORAN, C. (2003). Spatial reversal as a measure of executive functioning in children with autism. *The Journal of genetic psychology*. 164(1): 29-41.

CORBETT, B. A. & CONSTANTINE, L. J. (2006). Autism and Attention Deficit Hyperactivity Disorder: Assessing Attention and Response Control with the Integrated Visual and Auditory Continuous Performance Test. *Child Neuropsychology*. 12(4-5): 335-348.

CORBETT, B. A., CONSTANTINE, L. J., HENDREN, R., ROCKE, D. & OZONOFF, S. (2009). Examining executive functioning in children with autism spectrum disorder, attention deficit hyperactivity disorder and typical development. *Psychiatry Research*. 166(2–3): 210-222.

CORBETTA, M., PATEL, G. & SHULMAN, G. L. (2008). The reorienting system of the human brain: from environment to theory of mind. *Neuron*. 58(3): 306-324.

CORBETTA, M. & SHULMAN, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience*. 3(3): 201-215.

COULL, J. T. (1998). Neural correlates of attention and arousal: insights from electrophysiology, functional neuroimaging and psychopharmacology. *Progress in Neurobiology*. 55(4): 343-361.

COULL, J. T. (2004). fMRI studies of temporal attention: allocating attention within, or towards, time. *Cognitive Brain Research*. 21(2): 216-226.

COURCHESNE, E. (1997). Brainstem, cerebellar and limbic neuroanatomical abnormalities in autism. *Current Opinion in Neurobiology*. 7(2): 269-278.

COURCHESNE, E. (2004). Brain development in autism: Early overgrowth followed by premature arrest of growth. *Mental retardation and developmental disabilities research reviews*. 10(2): 106-111.

COURCHESNE, E., CAMPBELL, K. & SOLSO, S. (2011). Brain growth across the life span in autism: Age-specific changes in anatomical pathology. *Brain Research*. 1380138-145.

COURCHESNE, E., CARPER, R. & AKSHOOMOFF, N. (2003). Evidence of brain overgrowth in the first year of life in autism. *JAMA*. 290(3): 337-344.

COURCHESNE, E., KARNS, C., DAVIS, H., ZICCARDI, R., CARPER, R., TIGUE, Z., CHISUM, H., MOSES, P., PIERCE, K. & LORD, C. (2001a). Unusual brain growth patterns in early life in patients with autistic disorder: an MRI study. *Neurology*. 57(2): 245-254.

COURCHESNE, E., KARNS, C. M., DAVIS, H. R., ZICCARDI, R., CARPER, R. A. & TIGUE, Z. D. (2001b). Unusual brain growth patterns in early life in patients with autistic disorder: an MRI study. *Neurology*. 57.

COURCHESNE, E., LINCOLN, A. J., YEUNG-COURCHESNE, R., ELMASIAN, R. & GRILLON, C. (1989). Pathophysiologic findings in nonretarded autism and receptive developmental language disorder. *Journal of Autism and Developmental Disorders*. 19(1): 1-17.

COURCHESNE, E., PIERCE, K., SCHUMANN, C. M., REDCAY, E., BUCKWALTER, J. A., KENNEDY, D. P. & MORGAN, J. (2007). Mapping Early Brain Development in Autism. *Neuron*. 56(2): 399-413.

COURCHESNE, E., REDCAY, E. & KENNEDY, D. P. (2004). The autistic brain: birth through adulthood. *Current opinion in neurology*. 17(4): 489-496 410.1097/1001.wco.0000137542.0000114610.b0000137544.

COURCHESNE, E., TOWNSEND, J., AKSHOOMOFF, N. A., SAITOH, O., YEUNG-COURCHESNE, R., LINCOLN, A. J., JAMES, H. E., HAAS, R. H., SCHREIBMAN, L. & LAU, L. (1994). Impairment in shifting attention in autistic and cerebellar patients. *Behavioral neuroscience*. 108(5): 848-865.

COURCHESNE , E., YEUNG-COURCHESNE , R., HESSELINK , J. R. & JERNIGAN , T. L. (1988). Hypoplasia of Cerebellar Vermal Lobules VI and VII in Autism. *New England Journal of Medicine*. 318(21): 1349-1354.

CRAIG, A. D. (2003). Interoception: the sense of the physiological condition of the body. *Curr Opin Neurbiol*. 13.

CRAIG, A. D. (2009). How do you feel--now? The anterior insula and human awareness. *Nat Rev Neurosci*. 10.

CRAIG, M. C., ZAMAN, S. H., DALY, E. M., CUTTER, W. J., ROBERTSON, D. M., HALLAHAN, B., TOAL, F., REED, S., AMBIKAPATHY, A. & BRAMMER, M. (2007). Women with autistic-spectrum disorder: magnetic resonance imaging study of brain anatomy. *The British Journal of Psychiatry*. 191(3): 224-228.

CRITCHFIELD, T. S. & KOLLINS, S. H. (2001). Temporal discounting: Basic research and the analysis of socially important behavior. *Journal of applied behavior analysis*. 34(1): 101-122.

CRITCHLEY, H. D., WIENS, S., ROTSHTEIN, P., ÖHMAN, A. & DOLAN, R. J. (2004). Neural systems supporting interoceptive awareness. *Nature neuroscience*. 7(2): 189-195.

CRONE, E. A. & VAN DER MOLEN, M. W. (2004). Developmental Changes in Real Life Decision Making: Performance on a Gambling Task Previously Shown to Depend on the Ventromedial Prefrontal Cortex. *Developmental Neuropsychology*. 25(3): 251-279.

CUBILLO, A., SMITH, A. B., BARRETT, N., GIAMPIETRO, V., BRAMMER, M. J., SIMMONS, A. & RUBIA, K. (2014). Shared and Drug-Specific Effects of Atomoxetine and Methylphenidate on Inhibitory Brain Dysfunction in Medication-Naive ADHD Boys. *Cerebral Cortex*. 24(1): 174-185.

CUI, J., GAO, D., CHEN, Y., ZOU, X. & WANG, Y. (2010). Working Memory in Early-School-Age Children with Asperger's Syndrome. *Journal of Autism and Developmental Disorders*. 40(8): 958-967.

D'CRUZ, A. M., MOSCONI, M. W., RAGOZZINO, M. E., COOK, E. H. & SWEENEY, J. A. (2016). Alterations in the functional neural circuitry supporting flexible choice behavior in autism spectrum disorders. *Transl Psychiatry*. 6e916.

D'MELLO, A. M., CROCETTI, D., MOSTOFSKY, S. H. & STOODLEY, C. J. (2015). Cerebellar gray matter and lobular volumes correlate with core autism symptoms. *NeuroImage: Clinical*. 7631-639.

DALLEY, JEFFREY W., EVERITT, BARRY J. & ROBBINS, TREVOR W. (2011). Impulsivity, Compulsivity, and Top-Down Cognitive Control. *Neuron*. 69(4): 680-694.

DALY, E., ECKER, C., HALLAHAN, B., DEELEY, Q., CRAIG, M., MURPHY, C., JOHNSTON, P., SPAIN, D., GILLAN, N. & GUDBRANDSEN, M. (2014). Response inhibition and serotonin in autism: a functional MRI study using acute tryptophan depletion. *Brain*. 137(9): 2600-2610.

DAMADIAN, R. (1971). Tumor detection by nuclear magnetic resonance. *Science*. 171(3976): 1151-1153.

DAMBACHER, F., SACK, A. T., LOBBESTAEL, J., ARNTZ, A., BRUGMAN, S. & SCHUHMANN, T. (2014). A network approach to response inhibition: dissociating functional connectivity of neural components involved in action

restraint and action cancellation. *European Journal of Neuroscience*. 39(5): 821-831.

DANIELMEIER, C., EICHELE, T., FORSTMANN, B. U., TITTGEMEYER, M. & ULLSPERGER, M. (2011). Posterior medial frontal cortex activity predicts post-error adaptations in task-related visual and motor areas. *The Journal of Neuroscience*. 31(5): 1780-1789.

DAWSON, G., BERNIER, R. & RING, R. H. (2012). Social attention: a possible early indicator of efficacy in autism clinical trials. *Journal of Neurodevelopmental Disorders*. 4(1): 1.

DAWSON, G., MUNSON, J., ESTES, A., OSTERLING, J., MCPARTLAND, J., TOTH, K., CARVER, L. & ABBOTT, R. (2002). Neurocognitive Function and Joint Attention Ability in Young Children with Autism Spectrum Disorder Versus Developmental Delay. *Child Development*. 73(2): 345-358.

DE VRIES, F. E., DE WIT, S. J., CATH, D. C., VAN DER WERF, Y. D., VAN DER BORDEN, V., VAN ROSSUM, T. B., VAN BALKOM, A. J. L. M., VAN DER WEE, N. J. A., VELTMAN, D. J. & VAN DEN HEUVEL, O. A. (2014). Compensatory Frontoparietal Activity During Working Memory: An Endophenotype of Obsessive-Compulsive Disorder. *Biological Psychiatry*. 76(11): 878-887.

DE VRIES, M. & GEURTS, H. M. (2014). Beyond individual differences: are working memory and inhibition informative specifiers within ASD? *Journal of Neural Transmission*. 121(9): 1183-1198.

DE WIT, S. J., DE VRIES, F. E., VAN DER WERF, Y. D., CATH, D. C., HESLENFELD, D. J., VELTMAN, E. M., VAN BALKOM, A. J., VELTMAN, D. J. & VAN DEN HEUVEL, O. A. (2012). Presupplementary motor area

hyperactivity during response inhibition: a candidate endophenotype of obsessive-compulsive disorder. *American Journal of Psychiatry*.

DECKERSBACH, T., SAVAGE, C. R., CURRAN, T., BOHNE, A., WILHELM, S., BAER, L., JENIKE, M. A. & RAUCH, S. L. (2002). A study of parallel implicit and explicit information processing in patients with obsessive-compulsive disorder. *American Journal of Psychiatry*. 159(10): 1780-1782.

DELL'OSSO, B., ALTAMURA, A. C., ALLEN, A., MARAZZITI, D. & HOLLANDER, E. (2006). Epidemiologic and clinical updates on impulse control disorders: a critical review. *European Archives of Psychiatry and Clinical Neuroscience*. 256(8): 464-475.

DELONG, M. R. (1990). Primate models of movement disorders of basal ganglia origin. *Trends in neurosciences*. 13(7): 281-285.

DEMURIE, E., ROEYERS, H., BAEYENS, D. & SONUGA-BARKE, E. (2012). Temporal discounting of monetary rewards in children and adolescents with ADHD and autism spectrum disorders. *Developmental science*. 15(6): 791-800.

DEMURIE, E., ROEYERS, H., BAEYENS, D. & SONUGA-BARKE, E. (2013). Domain-general and domain-specific aspects of temporal discounting in children with ADHD and autism spectrum disorders (ASD): A proof of concept study. *Research in Developmental Disabilities*. 34(6): 1870-1880.

DENYS, D., ZOHAR, J. & WESTENBERG, H. G. (2004). The role of dopamine in obsessive-compulsive disorder: preclinical and clinical evidence. *The Journal of clinical psychiatry*. 65(suppl 14): 11-17.

DERAMUS, T. P. & KANA, R. K. (2015). Anatomical likelihood estimation meta-analysis of grey and white matter anomalies in autism spectrum disorders. *NeuroImage: Clinical*. 7525-536.

DEWIT, S. J., ALONSO, P., SCHWEREN, L., MATAIX-COLS, D., LOCHNER, C., MENCHÓN, J. M., STEIN, D. J., FOUCHE, J.-P., SORIANO-MAS, C., SATO, J. R., HOEXTER, M. Q., DENYS, D., NAKAMAE, T., NISHIDA, S., KWON, J. S., JANG, J. H., BUSATTO, G. F., CARDONER, N., CATH, D. C., FUKUI, K., JUNG, W. H., KIM, S. N., MIGUEL, E. C., NARUMOTO, J., PHILLIPS, M. L., PUJOL, J., REMIJNSE, P. L., SAKAI, Y., SHIN, N. Y., YAMADA, K., VELTMAN, D. J. & HEUVEL, O. A. V. D. (2014). Multicenter Voxel-Based Morphometry Mega-Analysis of Structural Brain Scans in Obsessive-Compulsive Disorder. *American Journal of Psychiatry*. 171(3): 340-349.

DI MARTINO, A., ROSS, K., UDDIN, L. Q., SKLAR, A. B., CASTELLANOS, F. X. & MILHAM, M. P. (2009). Functional Brain Correlates of Social and Nonsocial Processes in Autism Spectrum Disorders: An Activation Likelihood Estimation Meta-Analysis. *Biological Psychiatry*. 65(1): 63-74.

DICHTER, G. S. (2012). Functional magnetic resonance imaging of autism spectrum disorders. *Dialogues Clin Neurosci*. 14(3): 319-351.

DICHTER, G. S. & BELGER, A. (2007). Social stimuli interfere with cognitive control in autism. *NeuroImage*. 35(3): 1219-1230.

DICHTER, G. S., DAMIANO, C. A. & ALLEN, J. A. (2012a). Reward circuitry dysfunction in psychiatric and neurodevelopmental disorders and genetic syndromes: animal models and clinical findings. *Journal of Neurodevelopmental Disorders*. 4(1): 1.

DICHTER, G. S., FELDER, J. N., GREEN, S. R., RITTENBERG, A. M., SASSON, N. J. & BODFISH, J. W. (2012b). Reward circuitry function in autism spectrum disorders. *Social Cognitive and Affective Neuroscience*. 7(2): 160-172.

DICHTER, G. S., FELDER, J. N., GREEN, S. R., RITTENBERG, A. M., SASSON, N. J. & BODFISH, J. W. (2012c). Reward circuitry function in autism spectrum disorders. *Soc Cogn Affect Neruosci*. 42.

DICHTER, G. S., RICHEY, J. A., RITTENBERG, A. M., SABATINO, A. & BODFISH, J. W. (2012d). Reward Circuitry Function in Autism During Face Anticipation and Outcomes. *Journal of Autism and Developmental Disorders*. 42(2): 147-160.

DICKSTEIN, D. P., PESCOSOLIDO, M. F., REIDY, B. L., GALVAN, T., KIM, K. L., SEYMOUR, K. E., LAIRD, A. R., DI MARTINO, A. & BARRETT, R. P. (2013). Developmental Meta-Analysis of the Functional Neural Correlates of Autism Spectrum Disorders. *Journal of the American Academy of Child & Adolescent Psychiatry*. 52(3): 279-289.

DICKSTEIN, S. G., BANNON, K., XAVIER CASTELLANOS, F. & MILHAM, M. P. (2006). The neural correlates of attention deficit hyperactivity disorder: an ALE meta-analysis. *Journal of Child Psychology and Psychiatry*. 47(10): 1051-1062.

DIEDRICHSEN, J., VERSTYNEN, T., LEHMAN, S. L. & IVRY, R. B. (2005). Cerebellar Involvement in Anticipating the Consequences of Self-Produced Actions During Bimanual Movements. *Journal of Neurophysiology*. 93(2): 801-812.

DIWADKAR, V. A., BURGESS, A., HONG, E., RIX, C., ARNOLD, P. D., HANNA, G. L. & ROSENBERG, D. R. (2015). Dysfunctional activation and brain network profiles in youth with obsessive-compulsive disorder: a focus on the dorsal anterior cingulate during working memory. *Frontiers in Human Neuroscience*. 9.

DOSHI-VELEZ, F., GE, Y. & KOHANE, I. (2014). Comorbidity Clusters in Autism Spectrum Disorders: An Electronic Health Record Time-Series Analysis. *Pediatrics*. 133(1): e54-e63.

DRUMMOND, S. P., BISCHOFF-GRETHE, A., DINGES, D. F., AYALON, L., MEDNICK, S. C. & MELOY, M. J. (2005). The neural basis of the psychomotor vigilance task. *Sleep*. 28(9): 1059-1068.

DUERDEN, E. G., TAYLOR, M. J., SOORYA, L. V., WANG, T., FAN, J. & ANAGNOSTOU, E. (2013). Neural correlates of inhibition of socially relevant stimuli in adults with autism spectrum disorder. *Brain Research*. 153380-90.

DWORZYNSKI, K., RONALD, A., BOLTON, P. & HAPPÉ, F. (2012). How Different Are Girls and Boys Above and Below the Diagnostic Threshold for Autism Spectrum Disorders? *Journal of the American Academy of Child & Adolescent Psychiatry*. 51(8): 788-797.

ECKER, C., ROCHA-REGO, V., JOHNSTON, P., MOURAO-MIRANDA, J., MARQUAND, A., DALY, E. M., BRAMMER, M. J., MURPHY, C. & MURPHY, D. G. (2010). Investigating the predictive value of whole-brain structural MR scans in autism: A pattern classification approach. *NeuroImage*. 49(1): 44-56.

ECKER, C., SUCKLING, J., DEONI, S. C., LOMBARDO, M. V., BULLMORE, E. T., BARON-COHEN, S., CATANI, M., JEZZARD, P., BARNES, A. & BAILEY, A. J. (2012). Brain anatomy and its relationship to behavior in adults with autism spectrum disorder: a multicenter magnetic resonance imaging study. *Archives of General Psychiatry*. 69(2): 195-209.

EKLUND, A., NICHOLS, T. E. & KNUTSSON, H. (2016). Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates. *Proceedings of the National Academy of Sciences*. 113(28): 7900-7905.

ELIASON, M. J. & RICHMAN, L. C. (1987). The continuous performance test in learning disabled and nondisabled children. *Journal of Learning Disabilities*. 20(10): 614-619.

ELLIOTT, R., FRISTON, K. J. & DOLAN, R. J. (2000). Dissociable neural responses in human reward systems. *The Journal of Neuroscience*. 20(16): 6159-6165.

ENG, G. K., SIM, K. & CHEN, S.-H. A. (2015). Meta-analytic investigations of structural grey matter, executive domain-related functional activations, and white matter diffusivity in obsessive compulsive disorder: An integrative review. *Neuroscience & Biobehavioral Reviews*. 52233-257.

ERSCHE, K. D., WILLIAMS, G. B., ROBBINS, T. W. & BULLMORE, E. T. (2013). Meta-analysis of structural brain abnormalities associated with stimulant drug dependence and neuroimaging of addiction vulnerability and resilience. *Current Opinion in Neurobiology*. 23(4): 615-624.

ETKIN, A., EGNER, T. & KALISCH, R. (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends in Cognitive Sciences*. 15(2): 85-93.

EUSTON, D. R., GRUBER, A. J. & MCNAUGHTON, B. L. (2012). The role of medial prefrontal cortex in memory and decision making. *Neuron*. 76(6): 1057-1070.

EXNER, C., ZETSCHE, U., MARTIN, V., RIEF, W. & JANSEN, A. (2012). Regional gray matter changes in obsessive–compulsive disorder: Relationship to clinical characteristics. *Psychiatry Research: Neuroimaging*. 202(1): 74-76.

FAJA, S. & DAWSON, G. (2015). Reduced delay of gratification and effortful control among young children with autism spectrum disorders. *Autism*. 19(1): 91-101.

FAJA, S., MURIAS, M., BEAUCHAINE, T. P. & DAWSON, G. (2013). Reward-Based Decision Making and Electrodermal Responding by Young Children with

Autism Spectrum Disorders during a Gambling Task. *Autism Research*. 6(6): 494-505.

FAN, J., BERNARDI, S., VAN DAM, N. T., ANAGNOSTOU, E., GU, X., MARTIN, L., PARK, Y., LIU, X., KOLEVZON, A., SOORYA, L., GRODBERG, D., HOLLANDER, E. & HOF, P. R. (2012). Functional deficits of the attentional networks in autism. *Brain and Behavior*. 2(5): 647-660.

FAN, J., MCCANDLISS, B. D., FOSSELLA, J., FLOMBAUM, J. I. & POSNER, M. I. (2005). The activation of attentional networks. *NeuroImage*. 26(2): 471-479.

FIGEE, M., PATTIJ, T., WILLUHN, I., LUIGJES, J., VAN DEN BRINK, W., GOUDRIAAN, A., POTENZA, M. N., ROBBINS, T. W. & DENYS, D. (2016). Compulsivity in obsessive–compulsive disorder and addictions. *European Neuropsychopharmacology*. 26(5): 856-868.

FIGEE, M., VINK, M., DE GEUS, F., VULINK, N., VELTMAN, D. J., WESTENBERG, H. & DENYS, D. (2011). Dysfunctional Reward Circuitry in Obsessive-Compulsive Disorder. *Biological Psychiatry*. 69(9): 867-874.

FINEBERG, N. A., CHAMBERLAIN, S. R., GOUDRIAAN, A. E., STEIN, D. J., VANDERSCHUREN, L. J. M. J., GILLAN, C. M., SHEKAR, S., GORWOOD, P. A. P. M., VOON, V., MOREIN-ZAMIR, S., DENYS, D., SAHAKIAN, B. J., MOELLER, F. G., ROBBINS, T. W. & POTENZA, M. N. (2014). New developments in human neurocognition: clinical, genetic, and brain imaging correlates of impulsivity and compulsivity. *CNS Spectrums*. 19(01): 69-89.

FINEBERG, N. A., POTENZA, M. N., CHAMBERLAIN, S. R., BERLIN, H. A., MENZIES, L., BECHARA, A., SAHAKIAN, B. J., ROBBINS, T. W., BULLMORE, E. T. & HOLLANDER, E. (2009). Probing Compulsive and Impulsive Behaviors, from Animal Models to Endophenotypes: A Narrative Review. *Neuropsychopharmacology*. 35(3): 591-604.

FINGER, E. C., MARSH, A. A., MITCHELL, D. G., REID, M. E., SIMS, C., BUDHANI, S., KOSSON, D. S., CHEN, G., TOWBIN, K. E. & LEIBENLUFT, E. (2008). Abnormal ventromedial prefrontal cortex function in children with psychopathic traits during reversal learning. *Archives of General Psychiatry*. 65(5): 586-594.

FITZGERALD, K. D., STERN, E. R., ANGSTADT, M., NICHOLSON-MUTH, K. C., MAYNOR, M. R., WELSH, R. C., HANNA, G. L. & TAYLOR, S. F. (2010). Altered Function and Connectivity of the Medial Frontal Cortex in Pediatric Obsessive-Compulsive Disorder. *Biological Psychiatry*. 68(11): 1039-1047.

FITZGERALD, K. D., WELSH, R. C., GEHRING, W. J., ABELSON, J. L., HIMLE, J. A., LIBERZON, I. & TAYLOR, S. F. (2005). Error-related hyperactivity of the anterior cingulate cortex in obsessive-compulsive disorder. *Biological Psychiatry*. 57(3): 287-294.

FOMBONNE, E. (2009). Epidemiology of pervasive developmental disorders. *Pediatric Research*. 65(6): 591-598.

FONTENELLE, L. F., MENDLOWICZ, M. V. & VERSIANI, M. (2006). The descriptive epidemiology of obsessive–compulsive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 30(3): 327-337.

FOSTER, N. E. V., DOYLE-THOMAS, K. A. R., TRYFON, A., OUIMET, T., ANAGNOSTOU, E., EVANS, A. C., ZWAIGENBAUM, L., LERCH, J. P., LEWIS, J. D. & HYDE, K. L. (2015). Structural Gray Matter Differences During Childhood Development in Autism Spectrum Disorder: A Multimetric Approach. *Pediatric Neurology*. 53(4): 350-359.

FOUCHE, J.-P., DU PLESSIS, S., HATTINGH, C., ROOS, A., LOCHNER, C., SORIANO-MAS, C., SATO, J. R., NAKAMAE, T., NISHIDA, S. & KWON, J. S. (2016). Cortical thickness in obsessive–compulsive disorder: multisite mega-

analysis of 780 brain scans from six centres. *The British Journal of Psychiatry*. bjp. bp. 115.164020.

FREITAG, C. M., KONRAD, C., HÄBERLEN, M., KLESER, C., VON GONTARD, A., REITH, W., TROJE, N. F. & KRICK, C. (2008). Perception of biological motion in autism spectrum disorders. *Neuropsychologia*. 46(5): 1480-1494.

FRIED, R., JOSHI, G., BHIDE, P., POPE, A., GALDO, M., KOSTER, A., CHAN, J., FARAONE, S. V. & BIEDERMAN, J. (2016). A study of the neuropsychological correlates in adults with high functioning autism spectrum disorders. *Acta Neuropsychiatrica*. FirstView1-10.

FRISTON, K. J., ROTSHTEIN, P., GENG, J. J., STERZER, P. & HENSON, R. N. (2006). A critique of functional localisers. *NeuroImage*. 30(4): 1077-1087.

FRITH, U. (1994). Autism and theory of mind in everyday life. *Social development*. 3(2): 108-124.

FULLANA, M. A., MATAIX-COLS, D., CASERAS, X., ALONSO, P., MANUEL MENCHÓN, J., VALLEJO, J. & TORRUBIA, R. (2004). High sensitivity to punishment and low impulsivity in obsessive-compulsive patients with hoarding symptoms. *Psychiatry Research*. 129(1): 21-27.

GABAY, A. S., RADUA, J., KEMPTON, M. J. & MEHTA, M. A. (2014). The Ultimatum Game and the brain: A meta-analysis of neuroimaging studies. *Neuroscience & Biobehavioral Reviews*. 47549-558.

GADGIL, M., PETERSON, E., TREGELLAS, J., HEPBURN, S. & ROJAS, D. C. (2013). Differences in global and local level information processing in autism: An fMRI investigation. *Psychiatry Research: Neuroimaging*. 213(2): 115-121.

GALLAGHER, H. L. & FRITH, C. D. (2003). Functional imaging of 'theory of mind'. *Trends in Cognitive Sciences*. 7(2): 77-83.

GARRETSON, H., FEIN, D. & WATERHOUSE, L. (1990). Sustained attention in children with autism. *Journal of Autism and Developmental Disorders*. 20(1): 101-114.

GELMAN, A., CARLIN, J. B., STERN, H. S. & RUBIN, D. B. (2014a). *Bayesian data analysis*. Chapman & Hall/CRC Boca Raton, FL, USA.

GELMAN, A., HWANG, J. & VEHTARI, A. (2014b). Understanding predictive information criteria for Bayesian models. *Statistics and Computing*. 24(6): 997-1016.

GEURTS, H. M., CORBETT, B. & SOLOMON, M. (2009). The paradox of cognitive flexibility in autism. *Trends in Cognitive Sciences*. 13(2): 74-82.

GEURTS, H. M., VAN DEN BERGH, S. F. W. M. & RUZZANO, L. (2014). Prepotent Response Inhibition and Interference Control in Autism Spectrum Disorders: Two Meta-Analyses. *Autism Research*. 7(4): 407-420.

GEURTS, H. M., VERTÉ, S., OOSTERLAAN, J., ROEYERS, H. & SERGEANT, J. A. (2004). How specific are executive functioning deficits in attention deficit hyperactivity disorder and autism? *Journal of Child Psychology and Psychiatry*. 45(4): 836-854.

GEURTS, H. M. & VISSERS, M. E. (2012). Elderly with autism: Executive functions and memory. *Journal of Autism and Developmental Disorders*. 42(5): 665-675.

GIEDD, J. N. & RAPOPORT, J. L. (2010). Structural MRI of Pediatric Brain Development: What Have We Learned and Where Are We Going? *Neuron*. 67(5): 728-734.

GILBERT, A. R., AKKAL, D., ALMEIDA, J. R. C., MATAIX-COLS, D., KALAS, C., DEVLIN, B., BIRMAHER, B. & PHILLIPS, M. L. (2009). Neural Correlates of Symptom Dimensions in Pediatric Obsessive-Compulsive Disorder: A

Functional Magnetic Resonance Imaging Study. *Journal of the American Academy of Child & Adolescent Psychiatry*. 48(9): 936-944.

GILBERT, A. R., KESHAVAN, M. S., DIWADKAR, V., NUTCHE, J., MACMASTER, F., EASTER, P. C., BUHAGIAR, C. J. & ROSENBERG, D. R. (2008a). Gray Matter Differences between Pediatric Obsessive-Compulsive Disorder Patients and High-Risk Siblings: A Preliminary Voxel-Based Morphometry Study. *Neuroscience Letters*. 435(1): 45-50.

GILBERT, A. R., MATAIX-COLS, D., ALMEIDA, J. R., LAWRENCE, N., NUTCHE, J., DIWADKAR, V., KESHAVAN, M. S. & PHILLIPS, M. L. (2008b). Brain structure and symptom dimension relationships in obsessive–compulsive disorder: a voxel-based morphometry study. *Journal of Affective Disorders*. 109(1): 117-126.

GILLAN, C. M., PAPMEYER, M., MOREIN-ZAMIR, S., SAHAKIAN, B. J., FINEBERG, N. A., ROBBINS, T. W. & WIT, S. D. (2011). Disruption in the Balance Between Goal-Directed Behavior and Habit Learning in Obsessive-Compulsive Disorder. *American Journal of Psychiatry*. 168(7): 718-726.

GILLAN, C. M. & ROBBINS, T. W. (2014). Goal-directed learning and obsessive–compulsive disorder. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*. 369(1655).

GLAHN, D. C., LAIRD, A. R., ELLISON-WRIGHT, I., THELEN, S. M., ROBINSON, J. L., LANCASTER, J. L., BULLMORE, E. & FOX, P. T. (2008). Meta-analysis of gray matter anomalies in schizophrenia: application of anatomic likelihood estimation and network analysis. *Biological Psychiatry*. 64(9): 774-781.

GODDARD, M., SWAAB, H., ROMBOUTS, S. R. B. & VAN RIJN, S. (2015). Neural systems for social cognition: gray matter volume abnormalities in boys at high

genetic risk of autism symptoms, and a comparison with idiopathic autism spectrum disorder. *European Archives of Psychiatry and Clinical Neuroscience*. 1-9.

GOLDBERG, M. C., SPINELLI, S., JOEL, S., PEKAR, J. J., DENCKLA, M. B. & MOSTOFSKY, S. H. (2011). Children with high functioning autism show increased prefrontal and temporal cortex activity during error monitoring. *Developmental Cognitive Neuroscience*. 1(1): 47-56.

GOMOT, M., BERNARD, F. A., DAVIS, M. H., BELMONTE, M. K., ASHWIN, C., BULLMORE, E. T. & BARON-COHEN, S. (2006). Change detection in children with autism: An auditory event-related fMRI study. *NeuroImage*. 29(2): 475-484.

GONÇALVES, Ó. F., SOUSA, S., MAIA, L., CARVALHO, S., LEITE, J., GANHO, A., FERNANDES-GONÇALVES, A., FRANK, B., POCINHO, F. & CARRACEDO, A. (2015). Inferior frontal gyrus white matter abnormalities in obsessive–compulsive disorder. *Neuroreport*. 26(9): 495-500.

GONZALEZ-GADEA, M. L., SIGMAN, M., RATTAZZI, A., LAVIN, C., RIVERA-REI, A., MARINO, J., MANES, F. & IBANEZ, A. (2016). Neural markers of social and monetary rewards in children with Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder. *Scientific reports*. 6.

GOODKIND, M., EICKHOFF, S. B., OATHES, D. J. & ET AL. (2015). Identification of a common neurobiological substrate for mental illness. *JAMA Psychiatry*. 72(4): 305-315.

GOODMAN, R. & SCOTT, S. (1999). Comparing the Strengths and Difficulties Questionnaire and the Child Behavior Checklist: Is Small Beautiful? *Journal of abnormal child psychology*. 27(1): 17-24.

GOODMAN, W. K., PRICE, L. H., RASMUSSEN, S. A. & ET AL. (1989). The yale-brown obsessive compulsive scale: Ii. validity. *Archives of General Psychiatry*. 46(11): 1012-1016.

GORDON, P. K. (1985). Allocation of attention in obsessional disorder. *British Journal of Clinical Psychology*. 24(2): 101-107.

GORI, I., GIULIANO, A., MURATORI, F., SAVIOZZI, I., OLIVA, P., TANCREDI, R., COSENZA, A., TOSETTI, M., CALDERONI, S. & RETICO, A. (2015). Gray Matter Alterations in Young Children with Autism Spectrum Disorders: Comparing Morphometry at the Voxel and Regional Level. *Journal of Neuroimaging*. 25(6): 866-874.

GRASSI, G., PALLANTI, S., RIGHI, L., FIGEE, M., MANTIONE, M., DENYS, D., PICCAGLIANI, D., ROSSI, A. & STRATTA, P. (2015). Think twice: Impulsivity and decision making in obsessive–compulsive disorder. *Journal of Behavioral Addictions*. 4(4): 263-272.

GRAYBIEL, A. M., RAUCH, SCOTT L. (2000). Toward a Neurobiology of Obsessive-Compulsive Disorder. *Neuron*. 28343-347.

GREIMEL, E., NEHRKORN, B., SCHULTE-RÜTHER, M., FINK, G. R., NICKL-JOCKSCHAT, T., HERPERTZ-DAHLMANN, B., KONRAD, K. & EICKHOFF, S. B. (2013). Changes in grey matter development in autism spectrum disorder. *Brain Structure and Function*. 218(4): 929-942.

GRIFFITH, E. M., PENNINGTON, B. F., WEHNER, E. A. & ROGERS, S. J. (1999). Executive functions in young children with autism. *Child Development*. 70(4): 817-832.

GROEN, W. B., BUITELAAR, J. K., VAN DER GAAG, R. J. & ZWIERS, M. P. (2011). Pervasive microstructural abnormalities in autism: a DTI study. *Journal of psychiatry & neuroscience: JPN*. 36(1): 32.

GRÜTZMANN, R., ENDRASS, T., KAUFMANN, C., ALLEN, E., EICHELE, T. & KATHMANN, N. (2014). Presupplementary Motor Area Contributes to Altered Error Monitoring in Obsessive-Compulsive Disorder. *Biological Psychiatry*.

GU, B.-M., PARK, J.-Y., KANG, D.-H., LEE, S. J., YOO, S. Y., JO, H. J., CHOI, C.-H., LEE, J.-M. & KWON, J. S. (2008). Neural correlates of cognitive inflexibility during task-switching in obsessive-compulsive disorder. *Brain*. 131(1): 155-164.

GUITART-MASIP, M., HUYS, Q. J. M., FUENTEMILLA, L., DAYAN, P., DUZEL, E. & DOLAN, R. J. (2012). Go and no-go learning in reward and punishment: Interactions between affect and effect. *NeuroImage*. 62(1): 154-166.

HA, S., SOHN, I.-J., KIM, N., SIM, H. J. & CHEON, K.-A. (2015). Characteristics of Brains in Autism Spectrum Disorder: Structure, Function and Connectivity across the Lifespan. *Experimental Neurobiology*. 24(4): 273-284.

HABER, S. N. & KNUTSON, B. (2010). The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology*. 35(1): 4-26.

HAIST, F., ADAMO, M., WESTERFIELD, M., COURCHESNE, E. & TOWNSEND, J. (2005). The functional neuroanatomy of spatial attention in autism spectrum disorder. *Developmental Neuropsychology*. 27(3): 425-458.

HALARI, R., SIMIC, M., PARIANTE, C. M., PAPADOPOULOS, A., CLEARE, A., BRAMMER, M., FOMBONNE, E. & RUBIA, K. (2009). Reduced activation in lateral prefrontal cortex and anterior cingulate during attention and cognitive control functions in medication- naïve adolescents with depression compared to controls. *Journal of Child Psychology and Psychiatry*. 50(3): 307-316.

HAN, J. Y., KANG, D.-H., GU, B.-M., JUNG, W. H., CHOI, J.-S., CHOI, C.-H., JANG, J. H. & KWON, J. S. (2011). Altered brain activation in ventral frontal-striatal regions following a 16-week pharmacotherapy in unmedicated

obsessive-compulsive disorder. *Journal of Korean medical science*. 26(5): 665-674.

HAPPÉ, F., BOOTH, R., CHARLTON, R. & HUGHES, C. (2006). Executive function deficits in autism spectrum disorders and attention-deficit/hyperactivity disorder: examining profiles across domains and ages. *Brain and Cognition*. 61(1): 25-39.

HAPPÉ, F. & FRITH, U. (2006). The weak coherence account: detail-focused cognitive style in autism spectrum disorders. *Journal of Autism and Developmental Disorders*. 36(1): 5-25.

HAPPÉ, F. G. (1997). Central coherence and theory of mind in autism: Reading homographs in context. *British journal of developmental psychology*. 15(1): 1-12.

HARDAN, A. Y., KILPATRICK, M., KESHAVAN, M. S. & MINSHEW, N. J. (2003). Motor Performance and Anatomic Magnetic Resonance Imaging (MRI) of the Basal Ganglia in Autism. *Journal of Child Neurology*. 18(5): 317-324.

HARKIN, B. & KESSLER, K. (2011). The role of working memory in compulsive checking and OCD: A systematic classification of 58 experimental findings. *Clinical Psychology Review*. 31(6): 1004-1021.

HART, H., RADUA, J., MATAIX-COLS, D. & RUBIA, K. (2012). Meta-analysis of fMRI studies of timing in attention-deficit hyperactivity disorder (ADHD). *Neuroscience & Biobehavioral Reviews*. 36(10): 2248-2256.

HART, H., RADUA, J., NAKAO, T., MATAIX-COLS, D. & RUBIA, K. (2013). Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: Exploring task-specific, stimulant medication, and age effects. *JAMA Psychiatry*. 70(2): 185-198.

HASHIMOTO, N., NAKAAKI, S., KAWAGUCHI, A., SATO, J., KASAI, H., NAKAMAE, T., NARUMOTO, J., MIYATA, J., FURUKAWA, T. A. &

MIMURA, M. (2014). Brain structural abnormalities in behavior therapy-resistant obsessive-compulsive disorder revealed by voxel-based morphometry. *Neuropsychiatric disease and treatment*. 101987-1996.

HASHIMOTO, T., MURAKAWA, K., MIYAZAKI, M., TAYAMA, M. & KURODA, Y. (1992). Magnetic resonance imaging of the brain structures in the posterior fossa in retarded autistic children. *Acta Paediatrica*. 81(12): 1030-1034.

HASHIMOTO, T., TAYAMA, M., MURAKAWA, K., YOSHIMOTO, T., MIYAZAKI, M., HARADA, M. & KURODA, Y. (1995). Development of the brainstem and cerebellum in autistic patients. *Journal of Autism and Developmental Disorders*. 25(1): 1-18.

HAYNES, J.-D., SAKAI, K., REES, G., GILBERT, S., FRITH, C. & PASSINGHAM, R. E. (2007). Reading Hidden Intentions in the Human Brain. *Current Biology*. 17(4): 323-328.

HAZLETT, H. C., POE, M., GERIG, G., SMITH, R. G., PROVENZALE, J., ROSS, A., GILMORE, J. & PIVEN, J. (2005). Magnetic resonance imaging and head circumference study of brain size in autism: birth through age 2 years. *Archives of General Psychiatry*. 62(12): 1366-1376.

HAZLETT, H. C., POE, M. D., GERIG, G., SMITH, R. G. & PIVEN, J. (2006). Cortical Gray and White Brain Tissue Volume in Adolescents and Adults with Autism. *Biological Psychiatry*. 59(1): 1-6.

HENSELER, I., GRUBER, O., KRAFT, S., KRICK, C., REITH, W. & FALKAI, P. (2008). Compensatory hyperactivations as markers of latent working memory dysfunctions in patients with obsessive–compulsive disorder: an fMRI study. *Journal of Psychiatry & Neuroscience : JPN*. 33(3): 209-215.

HIGGINS, J., PLATTS, A. & PICKMAN, S. (1996). Principles of Structural Magnetic Resonance Imaging. In *Brain Imaging in Psychiatry* (ed. S. Lewis and N. Higgins). Blackwell Science Ltd.: Cambridge.

HILL, E. L. (2004). Executive dysfunction in autism. *Trends in Cognitive Sciences*. 8(1): 26-32.

HINVEST, N. S., ELLIOTT, R., MCKIE, S. & ANDERSON, I. M. (2011). Neural correlates of choice behavior related to impulsivity and venturesomeness. *Neuropsychologia*. 49(9): 2311-2320.

HOEFFNER, E., MUKHERJI, S., SRINIVASAN, A. & QUINT, D. (2012). Neuroradiology back to the future: brain imaging. *American Journal of Neuroradiology*. 33(1): 5-11.

HOEXTER, M. Q., DOUGHERTY, D. D., SHAVITT, R. G., D'ALCANTE, C. C., DURAN, F. L. S., LOPES, A. C., DINIZ, J. B., BATISTUZZO, M. C., EVANS, K. C., BRESSAN, R. A., BUSATTO, G. F. & MIGUEL, E. C. (2013). Differential prefrontal gray matter correlates of treatment response to fluoxetine or cognitive-behavioral therapy in obsessive–compulsive disorder. *European Neuropsychopharmacology*. 23(7): 569-580.

HOLDEN, C. (2001). 'Behavioral'addictions: do they exist? *Science*. 294(5544): 980-982.

HOLLANDER, E., ANAGNOSTOU, E., CHAPLIN, W., ESPOSITO, K., HAZNEDAR, M. M., LICALZI, E., WASSERMAN, S., SOORYA, L. & BUCHSBAUM, M. (2005). Striatal volume on magnetic resonance imaging and repetitive behaviors in autism. *Biological Psychiatry*. 58(3): 226-232.

HOLLANDER, E., DOERNBERG, E., SHAVITT, R., WATERMAN, R. J., SORENI, N., VELTMAN, D. J., SAHAKIAN, B. J. & FINEBERG, N. A. (2016). The

cost and impact of compulsivity: A research perspective. *European Neuropsychopharmacology*. 26(5): 800-809.

HOLLANDER, E., KIM, S., KHANNA, S. & PALLANTI, S. (2007). Obsessive-compulsive disorder and obsessive-compulsive spectrum disorders: diagnostic and dimensional issues. *CNS Spectrums*. 12(S3): 5-13.

HOLLANDER, E., KING, A., DELANEY, K., SMITH, C. J. & SILVERMAN, J. M. (2003). Obsessive–compulsive behaviors in parents of multiplex autism families. *Psychiatry Research*. 117(1): 11-16.

HOLT, R., CHURA, L., LAI, M.-C., SUCKLING, J., VON DEM HAGEN, E., CALDER, A., BULLMORE, E., BARON-COHEN, S. & SPENCER, M. (2014). 'Reading the Mind in the Eyes': an fMRI study of adolescents with autism and their siblings. *Psychological Medicine*. 44(15): 3215-3227.

HOLTTUM, J. R., MINSHEW, N. J., SANDERS, R. S. & PHILLIPS, N. E. (1992). Magnetic resonance imaging of the posterior fossa in autism. *Biological Psychiatry*. 32(12): 1091-1101.

HOOPER, C. J., LUCIANA, M., CONKLIN, H. M. & YARGER, R. S. (2004). Adolescents' Performance on the Iowa Gambling Task: Implications for the Development of Decision Making and Ventromedial Prefrontal Cortex. *Developmental Psychology*. 40(6): 1148-1158.

HOU, J., SONG, L., ZHANG, W., WU, W., WANG, J., ZHOU, D., QU, W., GUO, J., GU, S., HE, M., XIE, B. & LI, H. (2013). Morphologic and Functional Connectivity Alterations of Corticostriatal and Default Mode Network in Treatment-Naïve Patients with Obsessive-Compulsive Disorder. *PLoS ONE*. 8(12): e83931.

HOUNSFIELD, G. N. (1973). Computerized transverse axial scanning (tomography): Part 1. Description of system. *The British journal of radiology*. 46(552): 1016-1022.

HUGDAHL, K., RAICHLE, M. E., MITRA, A. & SPECHT, K. (2015). On the existence of a generalized non-specific task-dependent network. *Frontiers in Human Neuroscience*. 9.

HUGHES, C., RUSSELL, J. & ROBBINS, T. W. (1994). Evidence for executive dysfunction in autism. *Neuropsychologia*. 32(4): 477-492.

HUIZENGA, H. M., CRONE, E. A. & JANSEN, B. J. (2007). Decision-making in healthy children, adolescents and adults explained by the use of increasingly complex proportional reasoning rules. *Developmental science*. 10(6): 814-825.

HUYS, Q. J. M., MAIA, T. V. & FRANK, M. J. (2016). Computational psychiatry as a bridge from neuroscience to clinical applications. *Nat Neurosci*. 19(3): 404-413.

HUYSER, C., VAN DEN HEUVEL, O. A., WOLTERS, L., DE HAAN, E., LINDAUER, R. & VELTMAN, D. J. (2014). A longitudinal VBM study in paediatric obsessive–compulsive disorder at 2-year follow-up after cognitive behavioural therapy. *The World Journal of Biological Psychiatry*. 15(6): 443-452.

HUYSER, C., VAN DEN HEUVEL, O. A., WOLTERS, L. H., DE HAAN, E., BOER, F. & VELTMAN, D. J. (2013). Increased orbital frontal gray matter volume after cognitive behavioural therapy in paediatric obsessive compulsive disorder. *The World Journal of Biological Psychiatry*. 14(4): 319-331.

HUYSER, C., VELTMAN, D. J., WOLTERS, L. H., DE HAAN, E. & BOER, F. (2010). Functional Magnetic Resonance Imaging During Planning Before and After Cognitive-Behavioral Therapy in Pediatric Obsessive-Compulsive

Disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 49(12): 1238-1248.e1235.

HUYSER, C., VELTMAN, D. J., WOLTERS, L. H., DE HAAN, E. & BOER, F. (2011). Developmental aspects of error and high-conflict-related brain activity in pediatric obsessive–compulsive disorder: a fMRI study with a Flanker task before and after CBT. *Journal of Child Psychology and Psychiatry*. 52(12): 1251-1260.

HYBEL, K. A., MORTENSEN, E. L., LAMBEK, R., THASTUM, M. & THOMSEN, P. H. (2016). Cool and Hot Aspects of Executive Function in Childhood Obsessive-Compulsive Disorder. *Journal of abnormal child psychology*. 1-11.

HYDE, K. L., SAMSON, F., EVANS, A. C. & MOTTRON, L. (2010). Neuroanatomical differences in brain areas implicated in perceptual and other core features of autism revealed by cortical thickness analysis and voxel-based morphometry. *Human Brain Mapping*. 31(4): 556-566.

IGELSTRÖM, K. M., WEBB, T. W. & GRAZIANO, M. S. A. (2016). Functional Connectivity Between the Temporoparietal Cortex and Cerebellum in Autism Spectrum Disorder. *Cerebral Cortex*.

INSEL, T., CUTHBERT, B., GARVEY, M., HEINSSEN, R., PINE, D. S., QUINN, K., SANISLOW, C. & WANG, P. (2010). Research Domain Criteria (RDoC): Toward a New Classification Framework for Research on Mental Disorders. *American Journal of Psychiatry*. 167(7): 748-751.

ITAHASHI, T., YAMADA, T., NAKAMURA, M., WATANABE, H., YAMAGATA, B., JIMBO, D., SHIODA, S., KURODA, M., TORIIZUKA, K., KATO, N. & HASHIMOTO, R. (2015). Linked alterations in gray and white matter morphology in adults with high-functioning autism spectrum disorder: A multimodal brain imaging study. *NeuroImage: Clinical*. 7155-169.

IVARSSON, T. & MELIN, K. (2008). Autism spectrum traits in children and adolescents with obsessive-compulsive disorder (OCD). *Journal of Anxiety Disorders*. 22(6): 969-978.

JAAFARI, N., FRASCA, M., RIGALLEAU, F., RACHID, F., GIL, R., OLIÉ, J.-P., GUEHL, D., BURBAUD, P., AOUIZERATE, B. & ROTGÉ, J.-Y. (2013). Forgetting what you have checked: A link between working memory impairment and checking behaviors in obsessive-compulsive disorder. *European Psychiatry*. 28(2): 87-93.

JACK, A. & MORRIS, J. P. (2014). Neocerebellar contributions to social perception in adolescents with autism spectrum disorder. *Developmental Cognitive Neuroscience*. 1077-92.

JACOB, S., LANDEROS- WEISENBERGER, A. & LECKMAN, J. F. (2009). Autism spectrum and obsessive–compulsive disorders: OC behaviors, phenotypes and genetics. *Autism Research*. 2(6): 293-311.

JAYARAJAN, R. N., AGARWAL, S. M., VISWANATH, B., KALMADY, S. V., VENKATASUBRAMANIAN, G., SRINATH, S., CHANDRASHEKAR, C. R. & JANARDHAN REDDY, Y. C. (2015). A Voxel Based Morphometry Study of Brain Gray Matter Volumes in Juvenile Obsessive Compulsive Disorder. *Journal of the Canadian Academy of Child and Adolescent Psychiatry*. 24(2): 84-91.

JOHNSON, K. A., ROBERTSON, I. H., KELLY, S. P., SILK, T. J., BARRY, E., DÁIBHIS, A., WATCHORN, A., KEAVEY, M., FITZGERALD, M., GALLAGHER, L., GILL, M. & BELLGROVE, M. A. (2007). Dissociation in performance of children with ADHD and high-functioning autism on a task of sustained attention. *Neuropsychologia*. 45(10): 2234-2245.

JOHNSON, S. A., YECHIAM, E., MURPHY, R. R., QUELLER, S. & STOUT, J. C. (2006). Motivational processes and autonomic responsivity in Asperger's disorder: Evidence from the Iowa Gambling Task. *Journal of the International Neuropsychological Society*. 12(05): 668-676.

JOSEPH, R. M., MCGRATH, L. M. & TAGER-FLUSBERG, H. (2005a). Executive dysfunction and its relation to language ability in verbal school-age children with autism. *Developmental Neuropsychology*. 27(3): 361-378.

JOSEPH, R. M., STEELE, S. D., MEYER, E. & TAGER-FLUSBERG, H. (2005b). Self-ordered pointing in children with autism: failure to use verbal mediation in the service of working memory? *Neuropsychologia*. 43(10): 1400-1411.

JOSEPH, R. M. & TAGER–FLUSBERG, H. (2004). The relationship of theory of mind and executive functions to symptom type and severity in children with autism. *Development and psychopathology*. 16(1): 137-155.

JOU, R. J., MINSHEW, N. J., KESHAVAN, M. S., VITALE, M. P. & HARDAN, A. Y. (2010). Enlarged right superior temporal gyrus in children and adolescents with autism. *Brain Research*. 1360205-212.

JUCKEL, G., SCHLAGENHAUF, F., KOSLOWSKI, M., WÜSTENBERG, T., VILLRINGER, A., KNUTSON, B., WRASE, J. & HEINZ, A. (2006). Dysfunction of ventral striatal reward prediction in schizophrenia. *NeuroImage*. 29(2): 409-416.

JUNG, W., KANG, D. H., HAN, J., JANG, J., GU, B. M., CHOI, J. S., JUNG, M., CHOI, C. H. & KWON, J. (2011). Aberrant ventral striatal responses during incentive processing in unmedicated patients with obsessive–compulsive disorder. *Acta Psychiatrica Scandinavica*. 123(5): 376-386.

JURANEK, J., FILIPEK, P. A., BERENJI, G. R., MODAHL, C., OSANN, K. & SPENCE, M. A. (2006). Association Between Amygdala Volume and Anxiety

Level: Magnetic Resonance Imaging (MRI) Study in Autistic Children. *Journal of Child Neurology*. 21(12): 1051-1058.

JUST, M. A., CHERKASSKY, V. L., KELLER, T. A., KANA, R. K. & MINSHEW, N. J. (2007). Functional and Anatomical Cortical Underconnectivity in Autism: Evidence from an fMRI Study of an Executive Function Task and Corpus Callosum Morphometry. *Cerebral Cortex*. 17(4): 951-961.

JUST, M. A., KELLER, T. A., MALAVE, V. L., KANA, R. K. & VARMA, S. (2012). Autism as a neural systems disorder: A theory of frontal-posterior underconnectivity. *Neuroscience & Biobehavioral Reviews*. 36(4): 1292-1313.

KANA, R. K., KELLER, T. A., MINSHEW, N. J. & JUST, M. A. (2007). Inhibitory Control in High-Functioning Autism: Decreased Activation and Underconnectivity in Inhibition Networks. *Biological Psychiatry*. 62(3): 198-206.

KANA, R. K., LIBERO, L. E., HU, C. P., DESHPANDE, H. D. & COLBURN, J. S. (2014). Functional Brain Networks and White Matter Underlying Theory-of-Mind in Autism. *Social Cognitive and Affective Neuroscience*. 9(1): 98-105.

KANDEL, E. R., SCHWARTZ, J. H. & JESSELL, T. M. (2000). *Principles of neural science*. McGraw-hill New York.

KANG, D.-H., JANG, J. H., HAN, J. Y., KIM, J.-H., JUNG, W. H., CHOI, J.-S., CHOI, C.-H. & KWON, J. S. (2013). Neural correlates of altered response inhibition and dysfunctional connectivity at rest in obsessive–compulsive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 40340-346.

KANG, D.-H., KIM, J.-J., CHOI, J.-S., KIM, Y. I., KIM, C.-W., YOUN, T., HAN, M. H., CHANG, K.-H. & KWON, J. S. (2004). Volumetric investigation of the frontal-subcortical circuitry in patients with obsessive-compulsive disorder. *The Journal of neuropsychiatry and clinical neurosciences*. 16(3): 342-349.

KANNER, L. (1943). *Autistic disturbances of affective contact*.

KAUFMANN, C., BEUCKE, J., PREUSS, F., ENDRASS, T., SCHLAGENHAUF, F., HEINZ, A., JUCKEL, G. & KATHMANN, N. (2013). Medial prefrontal brain activation to anticipated reward and loss in obsessive–compulsive disorder. *NeuroImage: Clinical*. 2212-220.

KE, X., HONG, S., TANG, T., ZOU, B., LI, H., HANG, Y., ZHOU, Z., RUAN, Z., LU, Z. & TAO, G. (2008). Voxel-based morphometry study on brain structure in children with high-functioning autism. *Neuroreport*. 19(9): 921-925.

KEEHN, B., NAIR, A., LINCOLN, A. J., TOWNSEND, J. & MÜLLER, R.-A. (2016). Under-reactive but easily distracted: An fMRI investigation of attentional capture in autism spectrum disorder. *Developmental Cognitive Neuroscience*. 1746-56.

KEMPER, T. L. & BAUMAN, M. L. (1993). The contribution of neuropathologic studies to the understanding of autism. *Neurologic clinics*. 11(1): 175-187.

KENNEDY, D. P. & COURCHESNE, E. (2008). The intrinsic functional organization of the brain is altered in autism. *NeuroImage*. 39(4): 1877-1885.

KENNEDY, D. P., REDCAY, E. & COURCHESNE, E. (2006). Failing to deactivate: resting functional abnormalities in autism. *Proceedings of the National Academy of Sciences*. 103(21): 8275-8280.

KENWORTHY, L., BLACK, D. O., HARRISON, B., DELLA ROSA, A. & WALLACE, G. L. (2009). Are executive control functions related to autism symptoms in high-functioning children? *Child Neuropsychology*. 15(5): 425-440.

KERR, A. & ZELAZO, P. D. (2004). Development of "hot" executive function: The children's gambling task. *Brain and Cognition*. 55(1): 148-157.

KIM, H. W., KANG, J. I., NAMKOONG, K., JHUNG, K., HA, R. Y. & KIM, S. J. (2015a). Further evidence of a dissociation between decision-making under ambiguity and decision-making under risk in obsessive–compulsive disorder. *Journal of Affective Disorders*. 176118-124.

KIM, J.-J., LEE, M. C., KIM, J., KIM, I. Y., KIM, S. I., HAN, M. H., CHANG, K.-H. & KWON, J. S. (2001). Grey matter abnormalities in obsessive—compulsive disorder. *The British Journal of Psychiatry*. 179(4): 330-334.

KIM, K. W. & LEE, D. Y. (2002). Obsessive-compulsive disorder associated with a left orbitofrontal infarct. *The Journal of neuropsychiatry and clinical neurosciences*. 14(1): 88-89.

KIM, S.-G., JUNG, W. H., KIM, S. N., JANG, J. H. & KWON, J. S. (2015b). Alterations of Gray and White Matter Networks in Patients with Obsessive-Compulsive Disorder: A Multimodal Fusion Analysis of Structural MRI and DTI Using mCCA+jICA. *PLoS ONE*. 10(6): e0127118.

KIRBY, K. N. (2009). One-year temporal stability of delay-discount rates. *Psychonomic Bulletin & Review*. 16(3): 457-462.

KNECHT, S., DRÄGER, B., DEPPE, M., BOBE, L., LOHMANN, H., FLÖEL, A., RINGELSTEIN, E. B. & HENNINGSEN, H. (2000). Handedness and hemispheric language dominance in healthy humans. *Brain*. 123(12): 2512.

KNUTSON, B., ADAMS, C. M., FONG, G. W. & HOMMER, D. (2001). Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *J Neurosci*. 21.

KOCH, J. & EXNER, C. (2015). Selective attention deficits in obsessive-compulsive disorder: The role of metacognitive processes. *Psychiatry Research*. 225(3): 550-555.

KOCH, K., WAGNER, G., SCHACHTZABEL, C., PEIKERT, G., SCHULTZ, C. C., SAUER, H. & SCHLÖSSER, R. G. (2012). Aberrant anterior cingulate activation in obsessive–compulsive disorder is related to task complexity. *Neuropsychologia*. 50(5): 958-964.

KODAIRA, M., IWADARE, Y., USHIJIMA, H., OIJI, A., KATO, M., SUGIYAMA, N., SASAYAMA, D., USAMI, M., WATANABE, K. & SAITO, K. (2012). Poor performance on the Iowa gambling task in children with obsessive-compulsive disorder. *Annals of General Psychiatry*. 11(1): 25.

KOHLS, G., SCHULTE-RÜTHER, M., NEHRKORN, B., MÜLLER, K., FINK, G. R., KAMP-BECKER, I., HERPERTZ-DAHLMANN, B., SCHULTZ, R. T. & KONRAD, K. (2013). Reward system dysfunction in autism spectrum disorders. *Social Cognitive and Affective Neuroscience*. 8(5): 565-572.

KOPP, S. & GILLBERG, C. (1992). Girls with social deficits and learning problems: Autism, atypical Asperger syndrome or a variant of these conditions. *European Child & Adolescent Psychiatry*. 1(2): 89-99.

KOPŘIVOVÁ, J., HORÁČEK, J., TINTĚRA, J., PRAŠKO, J., RASZKA, M., IBRAHIM, I. & HÖSCHL, C. (2009). Medial frontal and dorsal cortical morphometric abnormalities are related to obsessive-compulsive disorder. *Neuroscience Letters*. 464(1): 62-66.

KOSAKA, H., OMORI, M., MUNESUE, T., ISHITOBI, M., MATSUMURA, Y., TAKAHASHI, T., NARITA, K., MURATA, T., SAITO, D. N. & UCHIYAMA, H. (2010). Smaller insula and inferior frontal volumes in young adults with pervasive developmental disorders. *NeuroImage*. 50(4): 1357-1363.

KOSHINO, H., CARPENTER, P. A., MINSHEW, N. J., CHERKASSKY, V. L., KELLER, T. A. & JUST, M. A. (2005). Functional connectivity in an fMRI working memory task in high-functioning autism. *NeuroImage*. 24(3): 810-821.

KRAIN, A. L., WILSON, A. M., ARBUCKLE, R., CASTELLANOS, F. X. & MILHAM, M. P. (2006). Distinct neural mechanisms of risk and ambiguity: A meta-analysis of decision-making. *NeuroImage*. 32(1): 477-484.

KRIETE, T. & NOELLE, D. C. (2015). Dopamine and the Development of Executive Dysfunction in Autism Spectrum Disorders. *PLoS ONE*. 10(3): e0121605.

KRISHNA, R., UDUPA, S., GEORGE, C. M., KUMAR, K. J., VISWANATH, B., KANDAVEL, T., VENKATASUBRAMANIAN, G. & REDDY, Y. J. (2011). Neuropsychological performance in OCD: a study in medication-naïve patients. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 35(8): 1969-1976.

KRUSCHKE, J. (2014). *Doing Bayesian data analysis: A tutorial with R, JAGS, and Stan*. Academic Press.

KUELZ, A. K., HOHAGEN, F. & VODERHOLZER, U. (2004). Neuropsychological performance in obsessive-compulsive disorder: a critical review. *Biological Psychology*. 65(3): 185-236.

KURTH, F., NARR, K. L., WOODS, R. P., O'NEILL, J., ALGER, J. R., CAPLAN, R., MCCRACKEN, J. T., TOGA, A. W. & LEVITT, J. G. (2011). Diminished Gray Matter Within the Hypothalamus in Autism Disorder: A Potential Link to Hormonal Effects? *Biological Psychiatry*. 70(3): 278-282.

KWON, H., OW, A. W., PEDATELLA, K. E., LOTSPEICH, L. J. & REISS, A. L. (2004). Voxel-based morphometry elucidates structural neuroanatomy of high-functioning autism and Asperger syndrome. *Developmental Medicine & Child Neurology*. 46(11): 760-764.

KWON, J., SHIN, Y., KIM, C., KIM, Y., YOUN, T., HAN, M., CHANG, K. & KIM, J. (2003). Similarity and disparity of obsessive-compulsive disorder and

schizophrenia in MR volumetric abnormalities of the hippocampus-amygdala complex. *Journal of Neurology, Neurosurgery & Psychiatry*. 74(7): 962-964.

KWON, J. S., JANG, J. H., CHOI, J.-S. & KANG, D.-H. (2009). Neuroimaging in obsessive-compulsive disorder.

LAI, C. L. E., LAU, Z., LUI, S. S., LOK, E., TAM, V., CHAN, Q., CHENG, K. M., LAM, S. M. & CHEUNG, E. F. (2016). Meta- analysis of neuropsychological measures of executive functioning in children and adolescents with high-functioning autism spectrum disorder. *Autism Research*.

LAMBRECQ, V., ROTGE, J. Y., JAAFARI, N., AOUIZERATE, B., LANGBOUR, N., BIOULAC, B., LIÉGEOIS-CHAUVEL, C., BURBAUD, P. & GUEHL, D. (2014). Differential role of visuospatial working memory in the propensity toward uncertainty in patients with obsessive–compulsive disorder and in healthy subjects. *Psychological Medicine*. 44(10): 2113-2124.

LANCASTER, J. L., TORDESILLAS-GUTIÉRREZ, D., MARTINEZ, M., SALINAS, F., EVANS, A., ZILLES, K., MAZZIOTTA, J. C. & FOX, P. T. (2007). Bias between MNI and Talairach coordinates analyzed using the ICBM-152 brain template. *Human Brain Mapping*. 28(11): 1194-1205.

LANDA, R. J. & GOLDBERG, M. C. (2005). Language, social, and executive functions in high functioning autism: A continuum of performance. *Journal of Autism and Developmental Disorders*. 35(5): 557-573.

LANDRY, O. & AL-TAIE, S. (2016). A Meta-analysis of the Wisconsin Card Sort Task in Autism. *Journal of Autism and Developmental Disorders*. 46(4): 1220-1235.

LANGE, N., TRAVERS, B. G., BIGLER, E. D., PRIGGE, M. B. D., FROEHLICH, A. L., NIELSEN, J. A., CARIELLO, A. N., ZIELINSKI, B. A., ANDERSON, J. S., FLETCHER, P. T., ALEXANDER, A. A. & LAINHART, J. E. (2015).

Longitudinal Volumetric Brain Changes in Autism Spectrum Disorder Ages 6–35 Years. *Autism Research*. 8(1): 82-93.

LANGEN, M., BOS, D., NOORDERMEER, S. D. S., NEDERVEEN, H., VAN ENGELAND, H. & DURSTON, S. (2014). Changes in the Development of Striatum Are Involved in Repetitive Behavior in Autism. *Biological Psychiatry*. 76(5): 405-411.

LANGEN, M., DURSTON, S., KAS, M. J., VAN ENGELAND, H. & STAAL, W. G. (2011). The neurobiology of repetitive behavior:… and men. *Neuroscience & Biobehavioral Reviews*. 35(3): 356-365.

LANGEN, M., LEEMANS, A., JOHNSTON, P., ECKER, C., DALY, E., MURPHY, C. M., DELL'ACQUA, F., DURSTON, S. & MURPHY, D. G. M. (2012). Fronto-striatal circuitry and inhibitory control in autism: Findings from diffusion tensor imaging tractography. *Cortex*. 48(2): 183-193.

LANGEN, M., SCHNACK, H. G., NEDERVEEN, H., BOS, D., LAHUIS, B. E., DE JONGE, M. V., VAN ENGELAND, H. & DURSTON, S. (2009). Changes in the developmental trajectories of striatum in autism. *Biological Psychiatry*. 66(4): 327-333.

LANGNER, R. & EICKHOFF, S. B. (2013). Sustaining Attention to Simple Tasks: A Meta-Analytic Review of the Neural Mechanisms of Vigilant Attention. *Psychol Bull*. 139(4): 870-900.

LAPLANE, D., LEVASSEUR, M., PILLON, B., DUBOIS, B., BAULAC, M., MAZOYER, B., DINH, S. T., SETTE, G., DANZE, F. & BARON, J. (1989). Obsessive-compulsive and other behavioural changes with bilateral basal ganglia lesions. *Brain*. 112(3): 699-725.

LAWRENCE, A. D., SAHAKIAN, B. J. & ROBBINS, T. W. (1998). Cognitive functions and corticostriatal circuits: insights from Huntington's disease. *Trends in Cognitive Sciences*. 2(10): 379-388.

LAWRENCE, N. S., JOLLANT, F., O'DALY, O., ZELAYA, F. & PHILLIPS, M. L. (2009). Distinct roles of prefrontal cortical subregions in the Iowa Gambling Task. *Cerebral Cortex*. 19(5): 1134-1143.

LAWRENCE, N. S., ROSS, T. J., HOFFMANN, R., GARAVAN, H. & STEIN, E. A. (2003). Multiple Neuronal Networks Mediate Sustained Attention. *Journal of Cognitive Neuroscience*. 15(7): 1028-1038.

LAWRENCE, N. S., WOODERSON, S., MATAIX-COLS, D., DAVID, R., SPECKENS, A. & PHILLIPS, M. L. (2006). Decision making and set shifting impairments are associated with distinct symptom dimensions in obsessive-compulsive disorder. *Neuropsychology*. 20(4): 409-419.

LÁZARO, L., BARGALLÓ, N., CASTRO-FORNIELES, J., FALCÓN, C., ANDRÉS, S., CALVO, R. & JUNQUÉ, C. (2009). Brain changes in children and adolescents with obsessive–compulsive disorder before and after treatment: A voxel-based morphometric MRI study. *Psychiatry Research: Neuroimaging*. 172(2): 140-146.

LÁZARO, L., CALDÚ, X., JUNQUÉ, C., BARGALLÓ, N., ANDRÉS, S., MORER, A. & CASTRO-FORNIELES, J. (2008). Cerebral activation in children and adolescents with obsessive–compulsive disorder before and after treatment: A functional MRI study. *Journal of Psychiatric Research*. 42(13): 1051-1059.

LÁZARO, L., CASTRO-FORNIELES, J., CULLELL, C., ANDRÉS, S., FALCÓN, C., CALVO, R. & BARGALLÓ, N. (2011). A voxel-based morphometric MRI study of stabilized obsessive–compulsive adolescent patients. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 35(8): 1863-1869.

LEDOUX, J. E. (2000). Emotion Circuits in the Brain. *Annual Review of Neuroscience*. 23(1): 155-184.

LEE, M. D. (2011). How cognitive modeling can benefit from hierarchical Bayesian models. *Journal of Mathematical Psychology*. 55(1): 1-7.

LEE, P. S., FOSS-FEIG, J., HENDERSON, J. G., KENWORTHY, L. E., GILOTTY, L., GAILLARD, W. D. & VAIDYA, C. J. (2007). Atypical neural substrates of Embedded Figures Task performance in children with Autism Spectrum Disorder. *NeuroImage*. 38(1): 184-193.

LEMON, J. M., GARGARO, B., ENTICOTT, P. G. & RINEHART, N. J. (2011). Brief report: Executive functioning in autism spectrum disorders: A gender comparison of response inhibition. *Journal of Autism and Developmental Disorders*. 41(3): 352-356.

LEVY, B. J. & WAGNER, A. D. (2011). Cognitive control and right ventrolateral prefrontal cortex: reflexive reorienting, motor inhibition, and action updating. *Annals of the New York Academy of Sciences*. 1224(1): 40-62.

LEYFER, O., FOLSTEIN, S., BACALMAN, S., DAVIS, N., DINH, E., MORGAN, J., TAGER-FLUSBERG, H. & LAINHART, J. (2006). Comorbid Psychiatric Disorders in Children with Autism: Interview Development and Rates of Disorders. *Journal of Autism and Developmental Disorders*. 36(7): 849-861.

LI, X., LU, Z.-L., D'ARGEMBEAU, A., NG, M. & BECHARA, A. (2010). The Iowa Gambling Task in fMRI Images. *Human Brain Mapping*. 31(3): 410-423.

LIBERO, L. E., DERAMUS, T. P., LAHTI, A. C., DESHPANDE, G. & KANA, R. K. (2015). Multimodal neuroimaging based classification of autism spectrum disorder using anatomical, neurochemical, and white matter correlates. *Cortex*. 6646-59.

LICHTER, D. G. & CUMMINGS, J. L. (2001). *Frontal-subcortical circuits in psychiatric and neurological disorders*. Guilford Press.

LIM, L., CHANTILUKE, K., CUBILLO, A. I., SMITH, A. B., SIMMONS, A., MEHTA, M. A. & RUBIA, K. (2015). Disorder-specific grey matter deficits in attention deficit hyperactivity disorder relative to autism spectrum disorder. *Psychological Medicine*. 45(05): 965-976.

LIM, L., RADUA, J. & RUBIA, K. (2014). Gray matter abnormalities in childhood maltreatment: a voxel-wise meta-analysis. *American Journal of Psychiatry*.

LIONELLO-DENOLF, K. M., MCILVANE, W. J., CANOVAS, D. S., DE SOUZA, D. G. & BARROS, R. S. (2008). Reversal learning set and functional equivalence in children with and without autism. *The Psychological Record*. 58(1): 15.

LIU, Y., HANNA, G. L., CARRASCO, M., GEHRING, W. J. & FITZGERALD, K. D. (2014). Altered relationship between electrophysiological response to errors and gray matter volumes in an extended network for error- processing in pediatric obsessive- compulsive disorder. *Human Brain Mapping*. 35(4): 1143-1153.

LOMBARDO, M. V., CHAKRABARTI, B., BULLMORE, E. T. & BARON-COHEN, S. (2011). Specialization of right temporo-parietal junction for mentalizing and its relation to social impairments in autism. *NeuroImage*. 56(3): 1832-1838.

LOPEZ, B. R., LINCOLN, A. J., OZONOFF, S. & LAI, Z. (2005). Examining the relationship between executive functions and restricted, repetitive symptoms of autistic disorder. *Journal of Autism and Developmental Disorders*. 35(4): 445-460.

LORD, C., RISI, S., LAMBRECHT, L., COOK, E., JR., LEVENTHAL, B., DILAVORE, P., PICKLES, A. & RUTTER, M. (2000). The Autism Diagnostic Observation Schedule—Generic: A Standard Measure of Social and

Communication Deficits Associated with the Spectrum of Autism. *Journal of Autism and Developmental Disorders*. 30(3): 205-223.

LORD, C., RUTTER, M. & COUTEUR, A. (1994). Autism Diagnostic Interview-Revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developmental Disorders*. 24(5): 659-685.

LORD, C., RUTTER, M., GOODE, S., HEEMSBERGEN, J., JORDAN, H. & MAWHOOD, L. (1989). Autism diagnostic observation schedule: a standardized observation of communicative and social behavior. *Journal of Autism and Developmental Disorders*. 19.

LOVELAND, K. A., BACHEVALIER, J., PEARSON, D. A. & LANE, D. M. (2008). Fronto-limbic functioning in children and adolescents with and without autism. *Neuropsychologia*. 46(1): 49-62.

LUCE, R. D. (1959). *Individual Choice Behavior: A Theoretical Analysis*. Wiley: New York.

LUKE, L., CLARE, I. C., RING, H., REDLEY, M. & WATSON, P. (2012). Decision-making difficulties experienced by adults with autism spectrum conditions. *Autism*. 16(6): 612-621.

LUNA, B., DOLL, S. K., HEGEDUS, S. J., MINSHEW, N. J. & SWEENEY, J. A. (2007). Maturation of executive function in autism. *Biological Psychiatry*. 61(4): 474-481.

LUNA, B., MINSHEW, N., GARVER, K., LAZAR, N., THULBORN, K., EDDY, W. & SWEENEY, J. (2002). Neocortical system abnormalities in autism An fMRI study of spatial working memory. *Neurology*. 59(6): 834-840.

MACDONALD, A., COHEN, J., STENGER, V. & CARTER, C. (2000). Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science*. 2881835 - 1838.

MAIA, T. V., COONEY, R. E. & PETERSON, B. S. (2008). The neural bases of obsessive–compulsive disorder in children and adults. *Development and psychopathology*. 20(04): 1251-1283.

MAK-FAN, K. M., TAYLOR, M. J., ROBERTS, W. & LERCH, J. P. (2012). Measures of Cortical Grey Matter Structure and Development in Children with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*. 42(3): 419-427.

MALTBY, N., TOLIN, D. F., WORHUNSKY, P., O'KEEFE, T. M. & KIEHL, K. A. (2005). Dysfunctional action monitoring hyperactivates frontal–striatal circuits in obsessive–compulsive disorder: an event-related fMRI study. *NeuroImage*. 24(2): 495-503.

MANJALY, Z. M., BRUNING, N., NEUFANG, S., STEPHAN, K. E., BRIEBER, S., MARSHALL, J. C., KAMP-BECKER, I., REMSCHMIDT, H., HERPERTZ-DAHLMANN, B. & KONRAD, K. (2007). Neurophysiological correlates of relatively enhanced local visual search in autistic adolescents. *NeuroImage*. 35(1): 283-291.

MANN, T. A. & WALKER, P. (2003). Autism and a deficit in broadening the spread of visual attention. *Journal of Child Psychology and Psychiatry*. 44(2): 274-284.

MARSH, R., HORGA, G., PARASHAR, N., WANG, Z., PETERSON, B. S. & SIMPSON, H. B. (2014). Altered activation in fronto-striatal circuits during sequential processing of conflict in unmedicated adults with obsessive-compulsive disorder. *Biological Psychiatry*. 75(8): 615-622.

MARTIN, A., PIGOTT, T. A., LALONDE, F. M., DALTON, I., DUBBERT, B. & MURPHY, D. L. (1993). Lack of evidence for Huntington's disease-like cognitive dysfunction in obsessive-compulsive disorder. *Biological Psychiatry*. 33(5): 345-353.

MARTONI, R. M., SALGARI, G., GALIMBERTI, E., CAVALLINI, M. C. & O'NEILL, J. (2015). Effects of gender and executive function on visuospatial working memory in adult obsessive–compulsive disorder. *European Archives of Psychiatry and Clinical Neuroscience*. 265(8): 707-718.

MASON, R. A., WILLIAMS, D. L., KANA, R. K., MINSHEW, N. & JUST, M. A. (2008). Theory of mind disruption and recruitment of the right hemisphere during narrative comprehension in autism. *Neuropsychologia*. 46(1): 269-280.

MATAIX-COLS, D., DO ROSARIO-CAMPOS, M. C. & LECKMAN, J. F. (2005). A multidimensional model of obsessive-compulsive disorder. *American Journal of Psychiatry*.

MATAIX-COLS, D., JUNQUÉ, C., VALLEJO, J., SÀNCHEZ-TURET, M., VERGER, K. & BARRIOS, M. (1997). Hemispheric functional imbalance in a sub-clinical obsessive-compulsive sample assessed by the Continuous Performance Test, Identical Pairs version. *Psychiatry Research*. 72(2): 115-126.

MATAIX-COLS, D. & VAN DEN HEUVEL, O. A. (2006). Common and Distinct Neural Correlates of Obsessive-Compulsive and Related Disorders. *Psychiatric Clinics of North America*. 29(2): 391-410.

MATAIX-COLS, D., WOODERSON, S., LAWRENCE, N., BRAMMER, M. J., SPECKENS, A. & PHILLIPS, M. L. (2004). Distinct Neural Correlates of Washing, Checking, and Hoarding SymptomDimensions in Obsessive-compulsive Disorder. *Archives of General Psychiatry*. 61(6): 564-576.

MATHIS, M. A. D., ALVARENGA, P. D., FUNARO, G., TORRESAN, R. C., MORAES, I., TORRES, A. R., ZILBERMAN, M. L. & HOUNIE, A. G. (2011). Gender differences in obsessive-compulsive disorder: a literature review. *Revista Brasileira de Psiquiatria*. 33(4): 390-399.

MATSUMOTO, R., ITO, H., TAKAHASHI, H., ANDO, T., FUJIMURA, Y., NAKAYAMA, K., OKUBO, Y., OBATA, T., FUKUI, K. & SUHARA, T. (2010). Reduced gray matter volume of dorsal cingulate cortex in patients with obsessive–compulsive disorder: A voxel-based morphometric study. *Psychiatry and Clinical Neurosciences*. 64(5): 541-547.

MAZZIOTTA, J. C., PHELPS, M. E. & PAHL, J. J. (1988). Cerebral glucose metabolic rates in nondepressed patients with obsessive compulsive disorder. *American Journal of Psychiatry*. 1451560-1563.

MCALONAN, G. M., CHEUNG, V., CHEUNG, C., SUCKLING, J., LAM, G. Y., TAI, K. S., YIP, L., MURPHY, D. G. M. & CHUA, S. E. (2005). Mapping the brain in autism. A voxel-based MRI study of volumetric differences and intercorrelations in autism. *Brain*. 128(2): 268-276.

MCALONAN, G. M., DALY, E., KUMARI, V., CRITCHLEY, H. D., VAN AMELSVOORT, T., SUCKLING, J., SIMMONS, A., SIGMUNDSSON, T., GREENWOOD, K. & RUSSELL, A. (2002). Brain anatomy and sensorimotor gating in Asperger's syndrome. *Brain*. 125(7): 1594-1606.

MCALONAN, G. M., SUCKLING, J., WONG, N., CHEUNG, V., LIENENKAEMPER, N., CHEUNG, C. & CHUA, S. E. (2008). Distinct patterns of grey matter abnormality in high-functioning autism and Asperger's syndrome. *Journal of Child Psychology and Psychiatry*. 49(12): 1287-1295.

MCCOY, A. N., CROWLEY, J. C., HAGHIGHIAN, G., DEAN, H. L. & PLATT, M. L. (2003). Saccade Reward Signals in Posterior Cingulate Cortex. *Neuron*. 40(5): 1031-1040.

MCEVOY, R. E., ROGERS, S. J. & PENNINGTON, B. F. (1993). Executive Function and Social Communication Deficits in Young Autistic Children. *Journal of Child Psychology and Psychiatry*. 34(4): 563-578.

MCGUIRE, P. K., BENCH, C. J., FRITH, C. D., MARKS, I. M., FRACKOWIAK, R. S. & DOLAN, R. J. (1994). Functional anatomy of obsessive-compulsive phenomena. *The British Journal of Psychiatry*. 164(4): 459-468.

MELLONI, M., URBISTONDO, C., SEDEÑO, L., GELORMINI, C., KICHIC, R. & IBANEZ, A. (2012). The extended fronto-striatal model of obsessive compulsive disorder: convergence from event-related potentials, neuropsychology and neuroimaging. *Frontiers in Human Neuroscience*. 6(259).

MENGOTTI, P., D'AGOSTINI, S., TERLEVIC, R., DE COLLE, C., BIASIZZO, E., LONDERO, D., FERRO, A., RAMBALDELLI, G., BALESTRIERI, M., ZANINI, S., FABBRO, F., MOLTENI, M. & BRAMBILLA, P. (2011). Altered white matter integrity and development in children with autism: A combined voxel-based morphometry and diffusion imaging study. *Brain Research Bulletin*. 84(2): 189-195.

MENON, V. & UDDIN, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Structure and Function*. 214(5): 655-667.

MENZIES, L., ACHARD, S., CHAMBERLAIN, S. R., FINEBERG, N., CHEN, C.-H., DEL CAMPO, N., SAHAKIAN, B. J., ROBBINS, T. W. & BULLMORE, E. (2007). Neurocognitive endophenotypes of obsessive-compulsive disorder. *Brain*. 130(12): 3223-3236.

MENZIES, L., CHAMBERLAIN, S. R., LAIRD, A. R., THELEN, S. M., SAHAKIAN, B. J. & BULLMORE, E. T. (2008). Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: The orbitofronto-striatal model revisited. *Neuroscience & Biobehavioral Reviews*. 32(3): 525-549.

MESULAM, M.-M. (1999). Spatial attention and neglect: parietal, frontal and cingulate contributions to the mental representation and attentional targeting of salient extrapersonal events. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*. 354(1387): 1325-1346.

MILLER, E. K. & COHEN, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience*. 24(1): 167-202.

MILLIERY, M., BOUVARD, M., AUPETIT, J. & COTTRAUX, J. (2000). Sustained attention in patients with obsessive–compulsive disorder: a controlled study. *Psychiatry Research*. 96(3): 199-209.

MINSHEW, N. J. & GOLDSTEIN, G. (2001). The pattern of intact and impaired memory functions in autism. *Journal of Child Psychology and Psychiatry*. 42(08): 1095-1101.

MINSHEW, N. J. & KELLER, T. A. (2010). The nature of brain dysfunction in autism: functional brain imaging studies. *Current opinion in neurology*. 23(2): 124.

MINSHEW, N. J., LUNA, B. & SWEENEY, J. A. (1999). Oculomotor evidence for neocortical systems but not cerebellar dysfunction in autism. *Neurology*. 52(5): 917-917.

MINSHEW, N. J., MUENZ, L. R., GOLDSTEIN, G. & PAYTON, J. B. (1992). Neuropsychological functioning in nonmentally retarded autistic individuals. *Journal of Clinical and Experimental Neuropsychology*. 14(5): 749-761.

MINSHEW, N. J. & WILLIAMS, D. L. (2007). The new neurobiology of autism: Cortex, connectivity, and neuronal organization. *Archives of Neurology*. 64(7): 945-950.

MITCHELL, S. R., REISS, A. L., TATUSKO, D. H., IKUTA, I., KAZMERSKI, D. B., BOTTI, J.-A. C., BURNETTE, C. P. & KATES, W. R. (2009). Neuroanatomic alterations and social and communication deficits in monozygotic twins discordant for autism disorder. *American Journal of Psychiatry*.

MIYAKE, A., FRIEDMAN, N. P., EMERSON, M. J., WITZKI, A. H., HOWERTER, A. & WAGER, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: A latent variable analysis. *Cognitive psychology*. 41(1): 49-100.

MIYAKE, Y., ONISHI, Y. & POPPEL, E. (2004). Two types of anticipation in synchronization tapping. *Acta neurobiologiae experimentalis*. 64(3): 415-426.

MOREIN-ZAMIR, S., CRAIG, K. J., ERSCHE, K. D., ABBOTT, S., MULLER, U., FINEBERG, N. A., BULLMORE, E. T., SAHAKIAN, B. J. & ROBBINS, T. W. (2010). Impaired visuospatial associative memory and attention in obsessive compulsive disorder but no evidence for differential dopaminergic modulation. *Psychopharmacology*. 212(3): 357-367.

MOREIN-ZAMIR, S., PAPMEYER, M., PERTUSA, A., CHAMBERLAIN, S. R., FINEBERG, N. A., SAHAKIAN, B. J., MATAIX-COLS, D. & ROBBINS, T. W. (2014). The profile of executive function in OCD hoarders and hoarding disorder. *Psychiatry Research*. 215(3): 659-667.

MOREIN-ZAMIR, S., VOON, V., DODDS, C. M., SULE, A., VAN NIEKERK, J., SAHAKIAN, B. J. & ROBBINS, T. W. (2015). Divergent subcortical activity for distinct executive functions: stopping and shifting in obsessive compulsive disorder. *Psychological Medicine*. FirstView1-12.

MOSCONI, M., ZWAIGENBAUM, L. & PIVEN, J. (2006). Structural MRI in autism: findings and future directions. *Clinical Neuroscience Research*. 6(3): 135-144.

MUELLER, S., KEESER, D., SAMSON, A. C., KIRSCH, V., BLAUTZIK, J., GROTHE, M., ERAT, O., HEGENLOH, M., COATES, U. & REISER, M. F. (2013). Convergent findings of altered functional and structural brain connectivity in individuals with high functioning autism: a multimodal MRI study. *PLoS ONE*. 8(6): e67329.

MUNSON, J., DAWSON, G., ABBOTT, R., FAJA, S., WEBB, S. J., FRIEDMAN, S. D., SHAW, D., ARTRU, A. & DAGER, S. R. (2006). Amygdalar volume and behavioral development in autism. *Archives of General Psychiatry*. 63(6): 686-693.

MURPHY, C. M., CHRISTAKOU, A., DALY, E. M., ECKER, C., GIAMPIETRO, V., BRAMMER, M., SMITH, A. B., JOHNSTON, P., ROBERTSON, D. M., CONSORTIUM, M. A., MURPHY, D. G. & RUBIA, K. (2014). Abnormal Functional Activation and Maturation of Fronto-Striato-Temporal and Cerebellar Regions During Sustained Attention in Autism Spectrum Disorder. *American Journal of Psychiatry*. 1711107-1116.

MURPHY, S. E. (2010). Using functional neuroimaging to investigate the mechanisms of action of selective serotonin reuptake inhibitors (SSRIs). *Current pharmaceutical design*. 16(18): 1990-1997.

MURPHY, S. E., LONGHITANO, C., AYRES, R. E., COWEN, P. J., HARMER, C. J. & ROGERS, R. D. (2008). The Role of Serotonin in Nonnormative Risky Choice: The Effects of Tryptophan Supplements on the “Reflection Effect” in Healthy Adult Volunteers. *Journal of Cognitive Neuroscience*. 21(9): 1709-1719.

MURRAY, K., JASSI, A., MATAIX-COLS, D., BARROW, F. & KREBS, G. (2015). Outcomes of cognitive behaviour therapy for obsessive–compulsive disorder in young people with and without autism spectrum disorders: A case controlled study. *Psychiatry Research*. 228(1): 8-13.

MUSSEY, J. L., TRAVERS, B. G., KLINGER, L. G. & KLINGER, M. R. (2015). Decision-Making Skills in ASD: Performance on the Iowa Gambling Task. *Autism Research*. 8(1): 105-114.

MYERSON, J., GREEN, L. & WARUSAWITHARANA, M. (2001). Area under the curve as a measure of discounting. *Journal of the Experimental Analysis of Behavior*. 76(2): 235-243.

MYUNG, I. J. (2003). Tutorial on maximum likelihood estimation. *Journal of Mathematical Psychology*. 47(1): 90-100.

NABEYAMA, M., NAKAGAWA, A., YOSHIURA, T., NAKAO, T., NAKATANI, E., TOGAO, O., YOSHIZATO, C., YOSHIOKA, K., TOMITA, M. & KANBA, S. (2008). Functional MRI study of brain activation alterations in patients with obsessive–compulsive disorder after symptom improvement. *Psychiatry Research: Neuroimaging*. 163(3): 236-247.

NAGAI, M., KISHI, K. & KATO, S. (2007). Insular cortex and neuropsychiatric disorders: A review of recent literature. *European Psychiatry*. 22(6): 387-394.

NAKAHACHI, T., IWASE, M., TAKAHASHI, H., HONAGA, E., SEKIYAMA, R., UKAI, S., ISHII, R., ISHIGAMI, W., KAJIMOTO, O., YAMASHITA, K. O., HASHIMOTO, R., TANII, H., SHIMIZU, A. & TAKEDA, M. (2006). Discrepancy of performance among working memory-related tasks in autism spectrum disorders was caused by task characteristics, apart from working memory, which could interfere with task execution. *Psychiatry and Clinical Neurosciences*. 60(3): 312-318.

NAKAO, T., NAKAGAWA, A., NAKATANI, E., NABEYAMA, M., SANEMATSU, H., YOSHIURA, T., TOGAO, O., TOMITA, M., MASUDA, Y. & YOSHIOKA, K. (2009a). Working memory dysfunction in obsessive–compulsive disorder: a neuropsychological and functional MRI study. *Journal of Psychiatric Research*. 43(8): 784-791.

NAKAO, T., NAKAGAWA, A., YOSHIURA, T., NAKATANI, E., NABEYAMA, M., SANEMATSU, H., TOGAO, O., YOSHIOKA, K., TOMITA, M. & KUROKI, T. (2009b). Duration effect of obsessive–compulsive disorder on cognitive function: a functional MRI study. *Depression and Anxiety*. 26(9): 814-823.

NAKAO, T., NAKAGAWA, A., YOSHIURA, T., NAKATANI, E., NABEYAMA, M., YOSHIZATO, C., KUDOH, A., TADA, K., YOSHIOKA, K. & KAWAMOTO, M. (2005). A functional MRI comparison of patients with obsessive–compulsive disorder and normal controls during a Chinese character Stroop task. *Psychiatry Research: Neuroimaging*. 139(2): 101-114.

NAKAO, T., OKADA, K. & KANBA, S. (2014). Neurobiological model of obsessive–compulsive disorder: Evidence from recent neuropsychological and neuroimaging findings. *Psychiatry and Clinical Neurosciences*. 68(8): 587-605.

NAKAO, T., RADUA, J., RUBIA, K. & MATAIX-COLS, D. (2011). Gray matter volume abnormalities in ADHD: voxel-based meta-analysis exploring the effects of age and stimulant medication. *American Journal of Psychiatry*. 168(11): 1154-1163.

NAVARI, S. & DAZZAN, P. (2009). Do antipsychotic drugs affect brain structure? A systematic and critical review of MRI findings. *Psychological Medicine*. 39(11): 1763.

NICKL-JOCKSCHAT, T., HABEL, U., MARIA MICHEL, T., MANNING, J., LAIRD, A. R., FOX, P. T., SCHNEIDER, F. & EICKHOFF, S. B. (2012). Brain

structure anomalies in autism spectrum disorder—a meta-analysis of VBM studies using anatomic likelihood estimation. *Human Brain Mapping*. 33(6): 1470-1489.

NIELEN, M., DEN BOER, J. & SMID, H. (2009). Patients with obsessive-compulsive disorder are impaired in associative learning based on external feedback. *Psychological Medicine*. 39(9): 1519.

NIELEN, M. M. A., VELTMAN, D. J., DE JONG, R., MULDER, G. & DEN BOER, J. A. (2002). Decision making performance in obsessive compulsive disorder. *Journal of Affective Disorders*. 69(1–3): 257-260.

NIKOLAUS, S., ANTKE, C., BEU, M. & MÜLLER, H.-W. (2010). Cortical GABA, striatal dopamine and midbrain serotonin as the key players in compulsive and anxiety disorders-results from in vivo imaging studies. *Reviews in the Neurosciences*. 21(2): 119-140.

NISHIDA, S., NARUMOTO, J., SAKAI, Y., MATSUOKA, T., NAKAMAE, T., YAMADA, K., NISHIMURA, T. & FUKUI, K. (2011). Anterior insular volume is larger in patients with obsessive–compulsive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 35(4): 997-1001.

NORDAHL, C. W., SCHOLZ, R., YANG, X., BUONOCORE, M. H., SIMON, T., ROGERS, S. & AMARAL, D. G. (2012). Increased rate of amygdala growth in children aged 2 to 4 years with autism spectrum disorders: a longitudinal study. *Archives of General Psychiatry*. 69(1): 53-61.

NORDAHL, T. E., BENKELFAT, C., SEMPLE, W. E. & GROSS, M. (1989). Cerebral glucose metabolic rates in obsessive compulsive disorder. *Neuropsychopharmacology*.

NOREIKA, V., FALTER, C. M. & RUBIA, K. (2013). Timing deficits in attention-deficit/hyperactivity disorder (ADHD): Evidence from neurocognitive and neuroimaging studies. *Neuropsychologia*. 51(2): 235-266.

NORMAN, L. J., CARLISI, C., LUKITO, S., HART, H., MATAIX-COLS, D., RADUA, J. & RUBIA, K. (2016). Structural and functional brain abnormalities in attention-deficit/hyperactivity disorder and obsessive-compulsive disorder: A comparative meta-analysis. *JAMA Psychiatry*. 73(8): 815-825.

O'HEARN, K., ASATO, M., ORDAZ, S. & LUNA, B. (2008). Neurodevelopment and executive function in autism. *Development and psychopathology*. 20(Special Issue 04): 1103-1132.

O'NIONS, E., SEBASTIAN, C. L., MCCRORY, E., CHANTILUKE, K., HAPPE, F. & VIDING, E. (2014). Neural bases of Theory of Mind in children with autism spectrum disorders and children with conduct problems and callous-unemotional traits. *Developmental science*. 17(5): 786-796.

ODUM, A. L. (2011). Delay discounting: Trait variable? *Behavioural Processes*. 87(1): 1-9.

OGAI, M., IYO, M., MORI, N. & TAKEI, N. (2005). A right orbitofrontal region and OCD symptoms: a case report. *Acta Psychiatrica Scandinavica*. 111(1): 74-76.

OGAWA, S., LEE, T.-M., KAY, A. R. & TANK, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences*. 87(24): 9868-9872.

OKADA, K., NAKAO, T., SANEMATSU, H., MURAYAMA, K., HONDA, S., TOMITA, M., TOGAO, O., YOSHIURA, T. & KANBA, S. (2015). Biological heterogeneity of obsessive–compulsive disorder: A voxel-based morphometric study based on dimensional assessment. *Psychiatry and Clinical Neurosciences*. 69(7): 411-421.

OLDFIELD, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*. 9(1): 97-113.

OLLEY, A., MALHI, G. & SACHDEV, P. (2007). Memory and executive functioning in obsessive–compulsive disorder: A selective review. *Journal of Affective Disorders*. 104(1–3): 15-23.

OOSTERLAAN, J., LOGAN, G. D. & SERGEANT, J. A. (1998). Response inhibition in AD/HD, CD, comorbid AD/HD+ CD, anxious, and control children: A meta-analysis of studies with the stop task. *Journal of Child Psychology and Psychiatry*. 39(03): 411-425.

ORNSTEIN, T. J., ARNOLD, P., MANASSIS, K., MENDLOWITZ, S. & SCHACHAR, R. (2010). Neuropsychological performance in childhood OCD: a preliminary study. *Depression and Anxiety*. 27(4): 372-380.

ORTUNO, F., OJEDA, N., ARBIZU, J., LOPEZ, P., MARTI-CLIMENT, J., PENUELAS, I. & CERVERA, S. (2002). Sustained attention in a counting task: normal performance and functional neuroanatomy. *NeuroImage*. 17(1): 411-420.

OWEN, A. M., MCMILLAN, K. M., LAIRD, A. R. & BULLMORE, E. (2005). N-back working memory paradigm: A meta- analysis of normative functional neuroimaging studies. *Human Brain Mapping*. 25(1): 46-59.

OZONOFF, S. (1995). Reliability and validity of the Wisconsin Card Sorting Test in studies of autism. *Neuropsychology*. 9(4): 491.

OZONOFF, S. (1997). Components of executive function in autism and other disorders.

OZONOFF, S., COOK, I., COON, H., DAWSON, G., JOSEPH, R. M., KLIN, A., MCMAHON, W. M., MINSHEW, N., MUNSON, J. A. & PENNINGTON, B. F. (2004). Performance on Cambridge Neuropsychological Test Automated Battery subtests sensitive to frontal lobe function in people with autistic

disorder: evidence from the Collaborative Programs of Excellence in Autism network. *Journal of Autism and Developmental Disorders*. 34(2): 139-150.

OZONOFF, S. & JENSEN, J. (1999). Brief Report: Specific Executive Function Profiles in Three Neurodevelopmental Disorders. *Journal of Autism and Developmental Disorders*. 29(2): 171-177.

OZONOFF, S. & MCEVOY, R. E. (1994). A longitudinal study of executive function and theory of mind development in autism. *Development and psychopathology*. 6(03): 415-431.

OZONOFF, S., PENNINGTON, B. F. & ROGERS, S. J. (1991). Executive Function Deficits in High-Functioning Autistic Individuals: Relationship to Theory of Mind. *Journal of Child Psychology and Psychiatry*. 32(7): 1081-1105.

OZONOFF, S., SOUTH, M. & MILLER, J. N. (2000). DSM-IV-defined Asperger syndrome: Cognitive, behavioral and early history differentiation from high-functioning autism. *Autism*. 4(1): 29-46.

OZONOFF, S. & STRAYER, D. L. (2001). Further Evidence of Intact Working Memory in Autism. *Journal of Autism and Developmental Disorders*. 31(3): 257-263.

PAGE, L. A., RUBIA, K., DEELEY, Q., DALY, E., TOAL, F., MATAIX-COLS, D., GIAMPIETRO, V., SCHMITZ, N. & MURPHY, D. G. (2009). A functional magnetic resonance imaging study of inhibitory control in obsessive-compulsive disorder. *Psychiatry Research: Neuroimaging*. 174(3): 202-209.

PALMEN, S. J., POL, H. E. H., KEMNER, C., SCHNACK, H. G., DURSTON, S., LAHUIS, B. E., KAHN, R. S. & VAN ENGELAND, H. (2005a). Increased gray-matter volume in medication-naive high-functioning children with autism spectrum disorder. *Psychological Medicine*. 35(04): 561-570.

PALMEN, S. J. M. C., HULSHOFF POL, H. E., KEMNER, C., SCHNACK, H. G., DURSTON, S., LAHUIS, B. E., KAHN, R. E. N., EACUTE, S & VAN ENGELAND, H. (2005b). Increased gray-matter volume in medication-naive high-functioning children with autism spectrum disorder. *Psychological Medicine*. 35(04): 561-570.

PANASITI, M. S., PUZZO, I. & CHAKRABARTI, B. (2016). Autistic Traits Moderate the Impact of Reward Learning on Social Behaviour. *Autism Research*. 9(4): 471-479.

PARASURAMAN, R. & YANTIS, S. (1998). *The attentive brain*. MIT Press Cambridge, MA.

PARRADO-HERNÁNDEZ, E., GÓMEZ-VERDEJO, V., MARTÍNEZ-RAMÓN, M., SHAWE-TAYLOR, J., ALONSO, P., PUJOL, J., MENCHÓN, J. M., CARDONER, N. & SORIANO-MAS, C. (2014). Discovering brain regions relevant to obsessive–compulsive disorder identification through bagging and transduction. *Medical Image Analysis*. 18(3): 435-448.

PASCUALVACA, D. M., FANTIE, B. D., PAPAGEORGIOU, M. & MIRSKY, A. F. (1998). Attentional Capacities in Children with Autism: Is There a General Deficit in Shifting Focus? *Journal of Autism and Developmental Disorders*. 28(6): 467-478.

PAULUS, M. P., ROGALSKY, C., SIMMONS, A., FEINSTEIN, J. S. & STEIN, M. B. (2003). Increased activation in the right insula during risk-taking decision making is related to harm avoidance and neuroticism. *NeuroImage*. 19(4): 1439-1448.

PECIÑA, S. (2008). Opioid reward 'liking' and 'wanting' in the nucleus accumbens. *Physiology & Behavior*. 94(5): 675-680.

PELLICANO, E., MAYBERY, M., DURKIN, K. & MALEY, A. (2006). Multiple cognitive capabilities/deficits in children with an autism spectrum disorder:"Weak" central coherence and its relationship to theory of mind and executive control. *Development and psychopathology*. 18(01): 77-98.

PENA-GARIJO, J., BARROS-LOSCERTALES, A., VENTURA-CAMPOS, N., RUIPÉREZ-RODRÍGUEZ, M., EDO-VILLAMON, S. & AVILA, C. (2011). Involvement of the thalamic-cortical-striatal circuit in patients with obsessive-compulsive disorder during an inhibitory control task with reward and punishment contingencies. *Revista de neurologia*. 53(2): 77-86.

PENADÉS, R., CATALÁN, R., ANDRÉS, S., SALAMERO, M. & GASTÓ, C. (2005). Executive function and nonverbal memory in obsessive-compulsive disorder. *Psychiatry Research*. 133(1): 81-90.

PENADÉS, R., CATALÁN, R., RUBIA, K., ANDRÉS, S., SALAMERO, M. & GASTÓ, C. (2007). Impaired response inhibition in obsessive compulsive disorder. *European Psychiatry*. 22(6): 404-410.

PENG, Z., LUI, S. S. Y., CHEUNG, E. F. C., JIN, Z., MIAO, G., JING, J. & CHAN, R. C. K. (2012). Brain structural abnormalities in obsessive-compulsive disorder: Converging evidence from white matter and grey matter. *Asian Journal of Psychiatry*. 5(4): 290-296.

PENNINGTON, B. F. & OZONOFF, S. (1996). Executive Functions and Developmental Psychopathology. *Journal of Child Psychology and Psychiatry*. 37(1): 51-87.

PETERS, J. & BÜCHEL, C. (2010). Episodic future thinking reduces reward delay discounting through an enhancement of prefrontal-mediotemporal interactions. *Neuron*. 66(1): 138-148.

PETERS, J. & BÜCHEL, C. (2011). The neural mechanisms of inter-temporal decision-making: understanding variability. *Trends in Cognitive Sciences*. 15(5): 227-239.

PETRIDES, M., ALIVISATOS, B., EVANS, A. C. & MEYER, E. (1993). Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. *Proceedings of the National Academy of Sciences*. 90(3): 873-877.

PHILIP, R. C. M., DAUVERMANN, M. R., WHALLEY, H. C., BAYNHAM, K., LAWRIE, S. M. & STANFIELD, A. C. (2012). A systematic review and meta-analysis of the fMRI investigation of autism spectrum disorders. *Neuroscience & Biobehavioral Reviews*. 36(2): 901-942.

PHILLIPS, M. L., DREVETS, W. C., RAUCH, S. L. & LANE, R. (2003). Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biological Psychiatry*. 54(5): 504-514.

PHILLIPS, M. L., MARKS, I. M., SENIOR, C., LYTHGOE, D., O'DWYER, A.-M., MEEHAN, O., WILLIAMS, S., BRAMMER, M., BULLMORE, E. & MCGUIRE, P. (2000). A differential neural response in obsessive–compulsive disorder patients with washing compared with checking symptoms to disgust. *Psychological Medicine*. 30(05): 1037-1050.

PIACENTINI, J. & BERGMAN, R. L. (2000). Obsessive-compulsive disorder in children. *Psychiatric Clinics of North America*. 23(3): 519-533.

PIERCE, K., GLAD, K. S. & SCHREIBMAN, L. (1997). Social Perception in Children with Autism: An Attentional Deficit? *Journal of Autism and Developmental Disorders*. 27(3): 265-282.

PINE, A., SEYMOUR, B., ROISER, J. P., BOSSAERTS, P., FRISTON, K. J., CURRAN, H. V. & DOLAN, R. J. (2009). Encoding of Marginal Utility across Time in the Human Brain. *The Journal of Neuroscience*. 29(30): 9575-9581.

PINE, D. S., GUYER, A. E., GOLDWIN, M., TOWBIN, K. A. & LEIBENLUFT, E. (2008). Autism spectrum disorder scale scores in pediatric mood and anxiety disorders. *Journal of the American Academy of Child & Adolescent Psychiatry*. 47(6): 652-661.

PINTO, A., STEINGLASS, J. E., GREENE, A. L., WEBER, E. U. & SIMPSON, H. B. (2014). Capacity to Delay Reward Differentiates Obsessive-Compulsive Disorder and Obsessive Compulsive Personality Disorder. *Biological Psychiatry*. 75(8): 653-659.

PIRAS, F., PIRAS, F., CHIAPPONI, C., GIRARDI, P., CALTAGIRONE, C. & SPALLETTA, G. (2015). Widespread structural brain changes in OCD: a systematic review of voxel-based morphometry studies. *Cortex*. 6289-108.

PIVEN, J., NEHME, E., SIMON, J., BARTA, P., PEARLSON, G. & FOLSTEIN, S. E. (1992). Magnetic resonance imaging in autism: measurement of the cerebellum, pons, and fourth ventricle. *Biological Psychiatry*. 31(5): 491-504.

POCHON, J.-B., RIIS, J., SANFEY, A. G., NYSTROM, L. E. & COHEN, J. D. (2008). Functional Imaging of Decision Conflict. *The Journal of Neuroscience*. 28(13): 3468-3473.

POLDRACK, R. A. (2007). Region of interest analysis for fMRI. *Social Cognitive and Affective Neuroscience*. 2(1): 67-70.

POLDRACK, R. A., MUMFORD, J. A. & NICHOLS, T. E. (2011). *Handbook of functional MRI data analysis*. Cambridge University Press.

POULIN-LORD, M.-P., BARBEAU, E. B., SOULIÈRES, I., MONCHI, O., DOYON, J., BENALI, H. & MOTTRON, L. (2014). Increased topographical variability of task-related activation in perceptive and motor associative regions in adult autistics. *NeuroImage: Clinical*. 4444-453.

POUSTKA, L., JENNEN-STEINMETZ, C., HENZE, R., VOMSTEIN, K., HAFFNER, J. & SIELTJES, B. (2012). Fronto-temporal disconnectivity and symptom severity in children with autism spectrum disorder. *The World Journal of Biological Psychiatry*. 13(4): 269-280.

PUJOL, J., SORIANO-MAS, C., ALONSO, P., CARDONER, N., MENCHÓN, J. M., DEUS, J. & VALLEJO, J. (2004). Mapping structural brain alterations in obsessive-compulsive disorder. *Archives of General Psychiatry*. 61(7): 720-730.

PURCELL, R., MARUFF, P., KYRIOS, M. & PANTELIS, C. (1998). Cognitive Deficits in Obsessive–Compulsive Disorder on Tests of Frontal–Striatal Function. *Biological Psychiatry*. 43(5): 348-357.

RACHMAN, S. (1997). A cognitive theory of obsessions. *Behav Res Ther*. 35(9): 793-802.

RADUA, J., GRAU, M., VAN DEN HEUVEL, O. A., THIEBAUT DE SCHOTTEN, M., STEIN, D. J., CANALES-RODRIGUEZ, E. J., CATANI, M. & MATAIX-COLS, D. (2014a). Multimodal Voxel-Based Meta-Analysis of White Matter Abnormalities in Obsessive-Compulsive Disorder. *Neuropsychopharmacology*. 39(7): 1547-1557.

RADUA, J. & MATAIX-COLS, D. (2009). Voxel-wise meta-analysis of grey matter changes in obsessive–compulsive disorder. *The British Journal of Psychiatry*. 195(5): 393-402.

RADUA, J., MATAIX-COLS, D., PHILLIPS, M. L., EL-HAGE, W., KRONHAUS, D. M., CARDONER, N. & SURGULADZE, S. (2012). A new meta-analytic method for neuroimaging studies that combines reported peak coordinates and statistical parametric maps. *European Psychiatry*. 27(8): 605-611.

RADUA, J., POZO, N. O. D., GÓMEZ, J., GUILLEN-GRIMA, F. & ORTUÑO, F. (2014b). Meta-analysis of functional neuroimaging studies indicates that an

increase of cognitive difficulty during executive tasks engages brain regions associated with time perception. *Neuropsychologia*. 58(0): 14-22.

RADUA, J., ROMEO, M., MATAIX-COLS, D. & FUSAR-POLI, P. (2013). A general approach for combining voxel-based meta-analyses conducted in different neuroimaging modalities. *Current medicinal chemistry*. 20(3): 462-466.

RADUA, J., RUBIA, K., CANALES-RODRÍGUEZ, E. J., POMAROL-CLOTET, E., FUSAR-POLI, P. & MATAIX-COLS, D. (2014c). Anisotropic kernels for coordinate-based meta-analyses of neuroimaging studies. *Frontiers in Psychiatry*. 5.

RADUA, J., VAN DEN HEUVEL, O. A., SURGULADZE, S. & MATAIX-COLS, D. (2010). Meta-analytical comparison of voxel-based morphometry studies in obsessive-compulsive disorder vs other anxiety disorders. *Archives of General Psychiatry*. 67(7): 701-711.

RAE, C. L., HUGHES, L. E., WEAVER, C., ANDERSON, M. C. & ROWE, J. B. (2014). Selection and stopping in voluntary action: A meta-analysis and combined fMRI study. *NeuroImage*. 86381-391.

RAHKO, J. S., VUONTELA, V. A., CARLSON, S., NIKKINEN, J., HURTIG, T. M., KUUSIKKO-GAUFFIN, S., MATTILA, M.-L., JUSSILA, K. K., REMES, J. J., JANSSON-VERKASALO, E. M., ARONEN, E. T., PAULS, D. L., EBELING, H. E., TERVONEN, O., MOILANEN, I. K. & KIVINIEMI, V. J. (2016). Attention and Working Memory in Adolescents with Autism Spectrum Disorder: A Functional MRI Study. *Child Psychiatry & Human Development*. 47(3): 503-517.

RAJENDER, G., BHATIA, M., KANWAL, K., MALHOTRA, S., SINGH, T. & CHAUDHARY, D. (2011). Study of neurocognitive endophenotypes in drug-

naïve obsessive–compulsive disorder patients, their first- degree relatives and healthy controls. *Acta Psychiatrica Scandinavica*. 124(2): 152-161.

RAO, N. P., REDDY, Y. J., KUMAR, K. J., KANDAVEL, T. & CHANDRASHEKAR, C. (2008). Are neuropsychological deficits trait markers in OCD? *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 32(6): 1574-1579.

RAPOPORT, J. L., SWEDO, S. E. & LEONARD, H. L. (1992). Childhood obsessive compulsive disorder. *Journal of Clinical Psychiatry*.

RASMUSSEN, S. A. & EISEN, J. L. (1992). The epidemiology and clinical features of obsessive compulsive disorder. *Psychiatric Clinics of North America*. 15(4): 743-758.

RAUCH, S. L., SAVAGE, C. R., ALPERT, N. M., DOUGHERTY, D., KENDRICK, A., CURRAN, T., BROWN, H. D., MANZO, P., FISCHMAN, A. J. & JENIKE, M. A. (1997a). Probing striatal function in obsessive-compulsive disorder: a PET study of implicit sequence learning. *Journal of Neuropsychiatry and Clinical Neurosciences*. 9(4): 568-573.

RAUCH, S. L., WHALEN, P. J., CURRAN, T., SHIN, L. M., COFFEY, B. J., SAVAGE, C. R., MCINERNEY, S. C., BAER, L. & JENIKE, M. A. (2000). Probing striato-thalamic function in obsessive-compulsive disorder and Tourette syndrome using neuroimaging methods. *Advances in neurology*. 85207-224.

RAUCH, S. L., WHALEN, P. J., SAVAGE, C. R., CURRAN, T., KENDRICK, A., BROWN, H. D., BUSH, G., BREITER, H. C. & ROSEN, B. R. (1997b). Striatal recruitment during an implicit sequence learning task as measured by functional magnetic resonance imaging. *Human Brain Mapping*. 5(2): 124-132.

RAUCH, S. L., WRIGHT, C. I., SAVAGE, C. R., MARTIS, B., MCMULLIN, K. G., WEDIG, M. M., GOLD, A. L. & KEUTHEN, N. J. (2007). Brain activation

during implicit sequence learning in individuals with trichotillomania. *Psychiatry Research: Neuroimaging*. 154(3): 233-240.

REDCAY, E. (2008). The superior temporal sulcus performs a common function for social and speech perception: implications for the emergence of autism. *Neuroscience & Biobehavioral Reviews*. 32(1): 123-142.

REDCAY, E. & COURCHESNE, E. (2005). When Is the Brain Enlarged in Autism? A Meta-Analysis of All Brain Size Reports. *Biological Psychiatry*. 58(1): 1-9.

REMIJNSE, P., NIELEN, M., VAN BALKOM, A., HENDRIKS, G., HOOGENDIJK, W., UYLINGS, H. & VELTMAN, D. (2009). Differential frontal-striatal and paralimbic activity during reversal learning in major depressive disorder and obsessive-compulsive disorder.

REMIJNSE, P. L., NIELEN, M., UYLINGS, H. & VELTMAN, D. J. (2005). Neural correlates of a reversal learning task with an affectively neutral baseline: an event-related fMRI study. *NeuroImage*. 26(2): 609-618.

REMIJNSE, P. L., NIELEN, M. M., VAN BALKOM, A. J., CATH, D. C., VAN OPPEN, P., UYLINGS, H. B. & VELTMAN, D. J. (2006). Reduced orbitofrontal-striatal activity on a reversal learning task in obsessive-compulsive disorder. *Archives of General Psychiatry*. 63(11): 1225-1236.

REMIJNSE, P. L., VAN DEN HEUVEL, O. A., NIELEN, M. M., VRIEND, C., HENDRIKS, G.-J., HOOGENDIJK, W. J. G., UYLINGS, H. B. & VELTMAN, D. J. (2013). Cognitive inflexibility in obsessive-compulsive disorder and major depression is associated with distinct neural correlates. *PLoS ONE*. 8(4): e59600.

RICCIO, C. A., REYNOLDS, C. R., LOWE, P. & MOORE, J. J. (2002). The continuous performance test: a window on the neural substrates for attention? *Archives of Clinical Neuropsychology*. 17(3): 235-272.

RICHARDS, J. B., MITCHELL, S. H., DE WIT, H. & SEIDEN, L. S. (1997). Determination of discount functions in rats with an adjusting-amount procedure. *Journal of the Experimental Analysis of Behavior*. 67(3): 353-366.

RICHARDS, J. B., ZHANG, L., MITCHELL, S. H. & WIT, H. (1999). Delay or probability discounting in a model of impulsive behavior: effect of alcohol. *Journal of the Experimental Analysis of Behavior*. 71(2): 121-143.

RICHEY, J. A., RITTENBERG, A., HUGHES, L., DAMIANO, C. R., SABATINO, A., MILLER, S., HANNA, E., BODFISH, J. W. & DICHTER, G. S. (2012). Common and distinct neural features of social and non-social reward processing in autism and social anxiety disorder. *Social Cognitive and Affective Neuroscience*. nss146.

RICHTER, J., HENZE, R., VOMSTEIN, K., STIELTJES, B., PARZER, P., HAFFNER, J., BRANDEIS, D. & POUSTKA, L. (2015). Reduced cortical thickness and its association with social reactivity in children with autism spectrum disorder. *Psychiatry Research: Neuroimaging*. 234(1): 15-24.

RIDDERINKHOF, K. R., VAN DEN WILDENBERG, W. P. M., SEGALOWITZ, S. J. & CARTER, C. S. (2004). Neurocognitive mechanisms of cognitive control: The role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning. *Brain and Cognition*. 56(2): 129-140.

RIEDEL, A., MAIER, S., ULBRICH, M., BISCALDI, M., EBERT, D., FANGMEIER, T., PERLOV, E. & TEBARTZ VAN ELST, L. (2014). No significant brain volume decreases or increases in adults with high-functioning autism spectrum disorder and above average intelligence: A voxel-based morphometric study. *Psychiatry Research: Neuroimaging*. 223(2): 67-74.

RIFFKIN, J., YÜCEL, M., MARUFF, P., WOOD, S. J., SOULSBY, B., OLVER, J., KYRIOS, M., VELAKOULIS, D. & PANTELIS, C. (2005). A manual and automated MRI study of anterior cingulate and orbito-frontal cortices, and caudate nucleus in obsessive-compulsive disorder: comparison with healthy controls and patients with schizophrenia. *Psychiatry Research: Neuroimaging*. 138(2): 99-113.

RING, H. A., BARON-COHEN, S., WHEELWRIGHT, S., WILLIAMS, S. C., BRAMMER, M., ANDREW, C. & BULLMORE, E. T. (1999). Cerebral correlates of preserved cognitive skills in autism. *Brain*. 122(7): 1305-1315.

RIVA, D., ANNUNZIATA, S., CONTARINO, V., ERBETTA, A., AQUINO, D. & BULGHERONI, S. (2013). Gray matter reduction in the vermis and CRUS-II Is associated with social and interaction deficits in low-functioning children with autistic spectrum disorders: a VBM-DARTEL study. *The Cerebellum*. 12(5): 676-685.

RIVA, D., BULGHERONI, S., AQUINO, D., DI SALLE, F., SAVOIARDO, M. & ERBETTA, A. (2011). Basal forebrain involvement in low-functioning autistic children: a voxel-based morphometry study. *American Journal of Neuroradiology*. 32(8): 1430-1435.

RIVET, T. T. & MATSON, J. L. (2011). Review of gender differences in core symptomatology in autism spectrum disorders. *Research in Autism Spectrum Disorders*. 5(3): 957-976.

ROBBINS, T. W., GILLAN, C. M., SMITH, D. G., DE WIT, S. & ERSCHE, K. D. (2012). Neurocognitive endophenotypes of impulsivity and compulsivity: towards dimensional psychiatry. *Trends in Cognitive Sciences*. 16(1): 81-91.

ROBINSON, E. B., LICHTENSTEIN, P., ANCKARSÄTER, H., HAPPÉ, F. & RONALD, A. (2013). Examining and interpreting the female protective effect

against autistic behavior. *Proceedings of the National Academy of Sciences*. 110(13): 5258-5262.

ROBINSON, S., GODDARD, L., DRITSCHEL, B., WISLEY, M. & HOWLIN, P. (2009). Executive functions in children with Autism Spectrum Disorders. *Brain and Cognition*. 71(3): 362-368.

ROCHA, F. F. D., ALVARENGA, N. B., MALLOY-DINIZ, L. & CORRÊA, H. (2011). Decision-making impairment in obsessive-compulsive disorder as measured by the Iowa Gambling Task. *Arquivos de neuro-psiquiatria*. 69(4): 642-647.

ROJAS, D. C., PETERSON, E., WINTERROWD, E., REITE, M. L., ROGERS, S. J. & TREGELLAS, J. R. (2006). Regional gray matter volumetric changes in autism associated with social and repetitive behavior symptoms. *BMC psychiatry*. 6(1): 56.

ROSENBERG, D. R. & KESHAVAN, M. S. (1998). Toward a Neurodevelopmental Model of Obsessive–Compulsive Disorder. *Biological Psychiatry*. 43(9): 623-640.

ROSVOLD, H. E., MIRSKY, A. F., SARASON, I., BRANSOME JR, E. D. & BECK, L. H. (1956). A continuous performance test of brain damage. *Journal of consulting psychology*. 20(5): 343.

ROTGE, J.-Y., GUEHL, D., DILHARREGUY, B., TIGNOL, J., BIOULAC, B., ALLARD, M., BURBAUD, P. & AOUIZERATE, B. (2009). Meta-analysis of brain volume changes in obsessive-compulsive disorder. *Biological Psychiatry*. 65(1): 75-83.

ROTGE, J.-Y., LANGBOUR, N., GUEHL, D., BIOULAC, B., JAAFARI, N., ALLARD, M., AOUIZERATE, B. & BURBAUD, P. (2010). Gray matter

alterations in obsessive–compulsive disorder: an anatomic likelihood estimation meta-analysis. *Neuropsychopharmacology*. 35(3): 686-691.

ROTGE, J.-Y. & TIGNOL, J. (2008). Provocation of obsessive-compulsive symptoms: a quantitative voxel-based meta-analysis of functional neuroimaging studies. *Journal of psychiatry & neuroscience: JPN*. 33(5): 405.

ROTH, R. M., SAYKIN, A. J., FLASHMAN, L. A., PIXLEY, H. S., WEST, J. D. & MAMOURIAN, A. C. (2007). Event-related functional magnetic resonance imaging of response inhibition in obsessive-compulsive disorder. *Biological Psychiatry*. 62(8): 901-909.

RUBIA, K. (2006). The neural correlates of timing functions. In *Timing the future: the case for a time-based prospective memory* (ed. J. Glicksohn), pp. 213-238. World Scientific Publishing: Hackensack, NJ.

RUBIA, K. (2011). "Cool" Inferior Frontostriatal Dysfunction in Attention-Deficit/Hyperactivity Disorder Versus "Hot" Ventromedial Orbitofrontal-Limbic Dysfunction in Conduct Disorder: A Review. *Biological Psychiatry*. 69(12): e69-e87.

RUBIA, K., ALEGRIA, A. A., CUBILLO, A. I., SMITH, A. B., BRAMMER, M. J. & RADUA, J. (2014). Effects of Stimulants on Brain Function in Attention-Deficit/Hyperactivity Disorder: A Systematic Review and Meta-Analysis. *Biological Psychiatry*. 76(8): 616-628.

RUBIA, K., CUBILLO, A., SMITH, A. B., WOOLLEY, J., HEYMAN, I. & BRAMMER, M. J. (2010a). Disorder-specific dysfunction in right inferior prefrontal cortex during two inhibition tasks in boys with attention-deficit hyperactivity disorder compared to boys with obsessive–compulsive disorder. *Human Brain Mapping*. 31(2): 287-299.

RUBIA, K., CUBILLO, A., WOOLLEY, J., BRAMMER, M. J. & SMITH, A. (2011). Disorder-specific dysfunctions in patients with attention-deficit/hyperactivity disorder compared to patients with obsessive-compulsive disorder during interference inhibition and attention allocation. *Human Brain Mapping*. 32(4): 601-611.

RUBIA, K., HALARI, R., CHRISTAKOU, A. & TAYLOR, E. (2009a). Impulsiveness as a timing disturbance: neurocognitive abnormalities in attention-deficit hyperactivity disorder during temporal processes and normalization with methylphenidate. *Philosophical Transactions of the Royal Society B: Biological Sciences*. 364(1525): 1919-1931.

RUBIA, K., HALARI, R., CUBILLO, A., MOHAMMAD, A.-M., BRAMMER, M. & TAYLOR, E. (2009b). Methylphenidate normalises activation and functional connectivity deficits in attention and motivation networks in medication-naïve children with ADHD during a rewarded continuous performance task. *Neuropharmacology*. 57(7–8): 640-652.

RUBIA, K., HYDE, Z., HALARI, R., GIAMPIETRO, V. & SMITH, A. (2010b). Effects of age and sex on developmental neural networks of visual–spatial attention allocation. *NeuroImage*. 51(2): 817-827.

RUBIA, K., LIM, L., ECKER, C., HALARI, R., GIAMPIETRO, V., SIMMONS, A., BRAMMER, M. & SMITH, A. (2013). Effects of age and gender on neural networks of motor response inhibition: From adolescence to mid-adulthood. *NeuroImage*. 83690-703.

RUBIA, K., OVERMEYER, S., TAYLOR, E., BRAMMER, M., WILLIAMS, S., SIMMONS, A., ANDREW, C. & BULLMORE, E. (1998). Prefrontal involvement in "temporal bridging" and timing movement. *Neuropsychologia*. 36(12): 1283-1293.

RUBIA, K., OVERMEYER, S., TAYLOR, E., BRAMMER, M., WILLIAMS, S. C. R., SIMMONS, A., ANDREW, C. & BULLMORE, E. T. (2000). Functional frontalisation with age: mapping neurodevelopmental trajectories with fMRI. *Neuroscience & Biobehavioral Reviews*. 24(1): 13-19.

RUBIA, K., SMITH, A. & TAYLOR, E. (2007). Performance of Children with Attention Deficit Hyperactivity Disorder (ADHD) on a Test Battery of Impulsiveness. *Child Neuropsychology*. 13276 - 304.

RUBIA, K., SMITH, A. B., HALARI, R., MATSUKURA, F., MOHAMMAD, M., TAYLOR, E. & BRAMMER, M. J. (2009c). Disorder-specific dissociation of orbitofrontal dysfunction in boys with pure conduct disorder during reward and ventrolateral prefrontal dysfunction in boys with pure ADHD during sustained attention. *The American Journal of Psychiatry*. 166(1): 83-94.

RUBIA, K., SMITH, A. B., WOOLLEY, J., NOSARTI, C., HEYMAN, I., TAYLOR, E. & BRAMMER, M. (2006). Progressive increase of frontostriatal brain activation from childhood to adulthood during event-related tasks of cognitive control. *Human Brain Mapping*. 27(12): 973-993.

RUSCIO, A., STEIN, D., CHIU, W. & KESSLER, R. (2010). The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. *Molecular psychiatry*. 15(1): 53-63.

RUSHWORTH, M. F., BUCKLEY, M. J., BEHRENS, T. E., WALTON, M. E. & BANNERMAN, D. M. (2007). Functional organization of the medial frontal cortex. *Current Opinion in Neurobiology*. 17(2): 220-227.

RUSSELL, A. J., MATAIX-COLS, D., ANSON, M. & MURPHY, D. G. M. (2005). Obsessions and compulsions in Asperger syndrome and high-functioning autism. *The British Journal of Psychiatry*. 186(6): 525-528.

RUSSELL, A. J., MURPHY, C. M., WILSON, E., GILLAN, N., BROWN, C., ROBERTSON, D. M., CRAIG, M. C., DEELEY, Q., ZINKSTOK, J., JOHNSTON, K., MCALONAN, G. M., SPAIN, D. & MURPHY, D. G. (2016). The mental health of individuals referred for assessment of autism spectrum disorder in adulthood: A clinic report. *Autism*. 20(5): 623-627.

RUSSELL, J. (1997). *Autism as an executive disorder*. Oxford University Press.

RUSSELL, J., JARROLD, C. & HENRY, L. (1996). Working memory in children with autism and with moderate learning difficulties. *Journal of Child Psychology and Psychiatry*. 37(6): 673-686.

RUSSELL, J., JARROLD, C. & HOOD, B. (1999). Two Intact Executive Capacities in Children with Autism: Implications for the Core Executive Dysfunctions in the Disorder. *Journal of Autism and Developmental Disorders*. 29(2): 103-112.

RUTTER, M., BAILEY, A. & LORD, C. (2003). *The social communication questionnaire: Manual*. Western Psychological Services: Los Angeles.

SACHDEV, P. S. & MALHI, G. S. (2005). Obsessive–compulsive behaviour: a disorder of decision- making. *Australian and New Zealand Journal of Psychiatry*. 39(9): 757-763.

SACHER, J., NEUMANN, J., OKON-SINGER, H., GOTOWIEC, S. & VILLRINGER, A. (2013). Sexual dimorphism in the human brain: evidence from neuroimaging. *Magnetic Resonance Imaging*. 31(3): 366-375.

SALIMI-KHORSHIDI, G., SMITH, S. M., KELTNER, J. R., WAGER, T. D. & NICHOLS, T. E. (2009). Meta-analysis of neuroimaging data: A comparison of image-based and coordinate-based pooling of studies. *NeuroImage*. 45(3): 810-823.

SALKOVSKIS, P. M. (1985). Obsessional-compulsive problems: A cognitive-behavioural analysis. *Behav Res Ther*. 23(5): 571-583.

SALKOVSKIS, P. M., WROE, A., GLEDHILL, A., MORRISON, N., FORRESTER, E., RICHARDS, C., REYNOLDS, M. & THORPE, S. (2000). Responsibility attitudes and interpretations are characteristic of obsessive compulsive disorder. *Behav Res Ther*. 38(4): 347-372.

SALMOND, C. H., ASHBURNER, J., CONNELLY, A., FRISTON, K. J., GADIAN, D. G. & VARGHA-KHADEM, F. (2005). The role of the medial temporal lobe in autistic spectrum disorders. *European Journal of Neuroscience*. 22(3): 764-772.

SANDERS, J., JOHNSON, K. A., GARAVAN, H., GILL, M. & GALLAGHER, L. (2008). A review of neuropsychological and neuroimaging research in autistic spectrum disorders: Attention, inhibition and cognitive flexibility. *Research in Autism Spectrum Disorders*. 2(1): 1-16.

SANDRINI, M., ROSSINI, P. M. & MINIUSSI, C. (2004). The differential involvement of inferior parietal lobule in number comparison: a rTMS study. *Neuropsychologia*. 42(14): 1902-1909.

SAXENA, S., BOTA, R. G. & BRODY, A. L. (2001). Brain-behavior relationships in obsessive-compulsive disorder. In *Seminars in clinical neuropsychiatry*, p. 82.

SAXENA, S., BRODY, A. L., SCHWARTZ, J. M. & BAXTER, L. R. (1998a). Neuroimaging and frontal-subcortical circuitry in obsessive-compulsive disorder. *The British Journal of Psychiatry*. 17326-37.

SAXENA, S., BRODY, A. L., SCHWARTZ, J. M. & BAXTER, L. R. (1998b). Neuroimaging and frontal-subcortical circuitry in obsessive-compulsive disorder. *The British Journal of Psychiatry*.

SAXENA, S. & RAUCH, S. L. (2000). Functional neuroimaging and the neuroanatomy of Obsessive-Compulsive Disorder. *Psychiatric Clinics of North America*. 23(3): 563-586.

SCAHILL, L., MCDOUGLE, C. J., WILLIAMS, S. K., DIMITROPOULOS, A., AMAN, M. G., MCCRACKEN, J. T., TIERNEY, E., ARNOLD, L. E., CRONIN, P., GRADOS, M., GHUMAN, J., KOENIG, K., LAM, K. S. L., MCGOUGH, J., POSEY, D. J., RITZ, L., SWIEZY, N. B. & VITIELLO, B. (2006). Children's Yale-Brown Obsessive Compulsive Scale Modified for Pervasive Developmental Disorders. *Journal of the American Academy of Child & Adolescent Psychiatry*. 45(9): 1114-1123.

SCAHILL, L., RIDDLE, M. A., MCSWIGGIN-HARDIN, M., ORT, S. I., KING, R. A., GOODMAN, W. K., CICCHETTI, D. & LECKMAN, J. F. (1997). Children's Yale-Brown obsessive compulsive scale: reliability and validity. *Journal of the American Academy of Child & Adolescent Psychiatry*. 36(6): 844-852.

SCHATZ, A. M., WEIMER, A. K. & TRAUNER, D. A. (2002). Brief Report: Attention Differences in Asperger Syndrome. *Journal of Autism and Developmental Disorders*. 32(4): 333-336.

SCHLÖSSER, R. G., WAGNER, G., SCHACHTZABEL, C., PEIKERT, G., KOCH, K., REICHENBACH, J. R. & SAUER, H. (2010). Fronto- cingulate effective connectivity in obsessive compulsive disorder: A study with fMRI and dynamic causal modeling. *Human Brain Mapping*. 31(12): 1834-1850.

SCHMIDTKE, K., SCHORB, A., WINKELMANN, G. & HOHAGEN, F. (1998). Cognitive frontal lobe dysfunction in obsessive-compulsive disorder. *Biological Psychiatry*. 43(9): 666-673.

SCHMITZ, N., RUBIA, K., DALY, E., SMITH, A., WILLIAMS, S. & MURPHY, D. G. M. (2006). Neural Correlates of Executive Function in Autistic Spectrum Disorders. *Biological Psychiatry*. 59(1): 7-16.

SCHMITZ, N., RUBIA, K., VAN AMELSVOORT, T., DALY, E., SMITH, A. & MURPHY, D. G. M. (2008). Neural correlates of reward in autism. *The British Journal of Psychiatry*. 192(1): 19-24.

SCHUMANN, C. M., BARNES, C. C., LORD, C. & COURCHESNE, E. (2009). Amygdala Enlargement in Toddlers with Autism Related to Severity of Social and Communication Impairments. *Biological Psychiatry*. 66(10): 942-949.

SCHUMANN, C. M., HAMSTRA, J., GOODLIN-JONES, B. L., LOTSPEICH, L. J., KWON, H., BUONOCORE, M. H., LAMMERS, C. R., REISS, A. L. & AMARAL, D. G. (2004). The amygdala is enlarged in children but not adolescents with autism; the hippocampus is enlarged at all ages. *The Journal of Neuroscience*. 24(28): 6392-6401.

SCOTT-VAN ZEELAND, A. A., DAPRETTO, M., GHAHREMANI, D. G., POLDRACK, R. A. & BOOKHEIMER, S. Y. (2010a). Reward processing in autism. *Autism Res*. 3.

SCOTT-VAN ZEELAND, A. A., DAPRETTO, M., GHAHREMANI, D. G., POLDRACK, R. A. & BOOKHEIMER, S. Y. (2010b). Reward processing in autism. *Autism Research*. 3(2): 53-67.

SHAFRAN, R. (2001). Obsessive- Compulsive Disorder in Children and Adolescents. *Child Psychology and Psychiatry Review*. 6(2): 50-58.

SHAFRITZ, K. M., BREGMAN, J. D., IKUTA, T. & SZESZKO, P. R. (2015). Neural systems mediating decision-making and response inhibition for social and nonsocial stimuli in autism. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 60112-120.

SHAFRITZ, K. M., DICHTER, G. S., BARANEK, G. T. & BELGER, A. (2008). The Neural Circuitry Mediating Shifts in Behavioral Response and Cognitive Set in Autism. *Biological Psychiatry*. 63(10): 974-980.

SHAH, A. & FRITH, U. (1983). An islet of ability in autistic children: A research note. *Journal of Child Psychology and Psychiatry*. 24(4): 613-620.

SHAMOSH, N. A., DEYOUNG, C. G., GREEN, A. E., REIS, D. L., JOHNSON, M. R., CONWAY, A. R., ENGLE, R. W., BRAVER, T. S. & GRAY, J. R. (2008). Individual differences in delay discounting relation to intelligence, working memory, and anterior prefrontal cortex. *Psychological Science*. 19(9): 904-911.

SHENHAV, A., BOTVINICK, M. M. & COHEN, J. D. (2013). The expected value of control: an integrative theory of anterior cingulate cortex function. *Neuron*. 79(2): 217-240.

SHIN, N. Y., LEE, T. Y., KIM, E. & KWON, J. S. (2014). Cognitive functioning in obsessive-compulsive disorder: a meta-analysis. *Psychological Medicine*. 44(06): 1121-1130.

SHIN, Y. W., KWON, J., KIM, J. J., KANG, D. H., YOUN, T., KANG, K., KANG, E., LEE, D. & LEE, M. (2006). Altered neural circuit for working memory before and after symptom provocation in patients with obsessive–compulsive disorder. *Acta Psychiatrica Scandinavica*. 113(5): 420-429.

SILK, T., RINEHART, N., BRADSHAW, J., TONGE, B., EGAN, G., O'BOYLE, M. & CUNNINGTON, R. (2006). Visuospatial processing and the function of prefrontal-parietal networks in autism spectrum disorders: a functional MRI study. *American Journal of Psychiatry*. 163(8): 1440-1443.

SIMMONS, A., MOORE, E. & WILLIAMS, S. C. (1999). Quality control for functional magnetic resonance imaging using automated data analysis and Shewhart charting. *Magnetic resonance in medicine*. 41(6): 1274-1278.

SIMON, D., ADLER, N., KAUFMANN, C. & KATHMANN, N. (2014). Amygdala hyperactivation during symptom provocation in obsessive–compulsive disorder and its modulation by distraction. *NeuroImage: Clinical*. 4549-557.

SIMON, D., KAUFMANN, C., MÜSCH, K., KISCHKEL, E. & KATHMANN, N. (2010). Fronto- striato- limbic hyperactivation in obsessive- compulsive disorder during individually tailored symptom provocation. *Psychophysiology*. 47(4): 728-738.

SIMONOFF, E., PICKLES, A., CHARMAN, T., CHANDLER, S., LOUCAS, T. & BAIRD, G. (2008). Psychiatric Disorders in Children With Autism Spectrum Disorders: Prevalence, Comorbidity, and Associated Factors in a Population-Derived Sample. *Journal of the American Academy of Child & Adolescent Psychiatry*. 47(8): 921-929.

SINGER, T., CRITCHLEY, H. D. & PREUSCHOFF, K. (2009). A common role of insula in feelings, empathy and uncertainty. *Trends in Cognitive Sciences*. 13(8): 334-340.

SKUSE, D. H. (2000). Imprinting, the X-chromosome, and the male brain: explaining sex differences in the liability to autism. *Pediatric Research*. 47(1): 9-9.

SMITH, A., TAYLOR, E., LIDZBA, K. & RUBIA, K. (2003). A right hemispheric frontocerebellar network for time discrimination of several hundreds of milliseconds. *NeuroImage*. 20(1): 344-350.

SMITH, A., TAYLOR, E., WARNER ROGERS, J., NEWMAN, S. & RUBIA, K. (2002). Evidence for a pure time perception deficit in children with ADHD. *Journal of Child Psychology and Psychiatry*. 43(4): 529-542.

SMITH, A. B., HALARI, R., GIAMPETRO, V., BRAMMER, M. & RUBIA, K. (2011). Developmental effects of reward on sustained attention networks. *NeuroImage*. 56(3): 1693-1704.

SMITH, D. G., XIAO, L. & BECHARA, A. (2012). Decision making in children and adolescents: impaired Iowa Gambling Task performance in early adolescence. *Developmental Psychology*. 48(4): 1180.

SMITH, S. M., JENKINSON, M., WOOLRICH, M. W., BECKMANN, C. F., BEHRENS, T. E., JOHANSEN-BERG, H., BANNISTER, P. R., DE LUCA, M., DROBNJAK, I. & FLITNEY, D. E. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*. 23S208-S219.

SMOSKI, M. J., FELDER, J., BIZZELL, J., GREEN, S. R., ERNST, M., LYNCH, T. R. & DICHTER, G. S. (2009). fMRI of alterations in reward selection, anticipation, and feedback in major depressive disorder. *Journal of Affective Disorders*. 118(1): 69-78.

SNYDER, H. R., KAISER, R. H., WARREN, S. L. & HELLER, W. (2014). Obsessive-Compulsive Disorder Is Associated With Broad Impairments in Executive Function: A Meta-Analysis. *Clinical Psychological Science*. 3(2): 301-330.

SOHN, M.-H., URSU, S., ANDERSON, J. R., STENGER, V. A. & CARTER, C. S. (2000). The role of prefrontal cortex and posterior parietal cortex in task switching. *Proceedings of the National Academy of Sciences*. 97(24): 13448-13453.

SOHN, S. Y., KANG, J. I., NAMKOONG, K. & KIM, S. J. (2014). Multidimensional measures of impulsivity in obsessive-compulsive disorder: Cannot wait and stop. *PLoS ONE*. 9(11): e111739.

SOLOMON, M., FRANK, M. J., RAGLAND, J. D., SMITH, A. C., NIENDAM, T. A., LESH, T. A., GRAYSON, D. S., BECK, J. S., MATTER, J. C. & CARTER, C. S. (2015). Feedback-driven trial-by-trial learning in autism spectrum disorders. *American Journal of Psychiatry*.

SOLOMON, M., OZONOFF, S. J., CUMMINGS, N. & CARTER, C. S. (2008). Cognitive control in autism spectrum disorders. *International journal of developmental neuroscience*. 26(2): 239-247.

SOLOMON, M., OZONOFF, S. J., URSU, S., RAVIZZA, S., CUMMINGS, N., LY, S. & CARTER, C. S. (2009). The neural substrates of cognitive control deficits in autism spectrum disorders. *Neuropsychologia*. 47(12): 2515-2526.

SOLOMON, M., YOON, J. H., RAGLAND, J. D., NIENDAM, T. A., LESH, T. A., FAIRBROTHER, W. & CARTER, C. S. (2014). The Development of the Neural Substrates of Cognitive Control in Adolescents with Autism Spectrum Disorders. *Biological Psychiatry*. 76(5): 412-421.

SONG, A., JUNG, W. H., JANG, J. H., KIM, E., SHIM, G., PARK, H. Y., CHOI, C.-H. & KWON, J. S. (2011). Disproportionate Alterations in the Anterior and Posterior Insular Cortices in Obsessive?Compulsive Disorder. *PLoS ONE*. 6(7): e22361.

SOOMRO, G. M., ALTMAN, D. G., RAJAGOPAL, S. & OAKLEY BROWNE, M. (2008). Selective serotonin re- uptake inhibitors (SSRIs) versus placebo for obsessive compulsive disorder (OCD). *The Cochrane Library*.

SORIANO-MAS, C., PUJOL, J., ALONSO, P., CARDONER, N., MENCHÓN, J. M., HARRISON, B. J., DEUS, J., VALLEJO, J. & GASER, C. (2007). Identifying patients with obsessive–compulsive disorder using whole-brain anatomy. *NeuroImage*. 35(3): 1028-1037.

SOUTH, M., CHAMBERLAIN, P. D., WIGHAM, S., NEWTON, T., LE COUTEUR, A., MCCONACHIE, H., GRAY, L., FREESTON, M., PARR, J., KIRWAN, C. B. & RODGERS, J. (2014). Enhanced decision making and risk avoidance in high-functioning autism spectrum disorder. *Neuropsychology*. 28(2): 222-228.

SOUTH, M., OZONOFF, S., SUCHY, Y., KESNER, R. P., MCMAHON, W. M. & LAINHART, J. E. (2008). Intact emotion facilitation for nonsocial stimuli in autism: is amygdala impairment in autism specific for social information? *Journal of the International Neuropsychological Society*. 14(01): 42-54.

SOWELL, E. R., THOMPSON, P. M., HOLMES, C. J., BATTH, R., JERNIGAN, T. L. & TOGA, A. W. (1999). Localizing age-related changes in brain structure between childhood and adolescence using statistical parametric mapping. *NeuroImage*. 9(6): 587-597.

SPALLETTA, G., PIRAS, F., FAGIOLI, S., CALTAGIRONE, C. & PIRAS, F. (2014). Brain microstructural changes and cognitive correlates in patients with pure obsessive compulsive disorder. *Brain and Behavior*. 4(2): 261-277.

SPARKS, B. F., FRIEDMAN, S. D., SHAW, D. W., AYLWARD, E. H., ECHELARD, D., ARTRU, A. A., MARAVILLA, K. R., GIEDD, J. N., MUNSON, J., DAWSON, G. & DAGER, S. R. (2002). Brain structural abnormalities in young children with autism spectrum disorder. *Neurology*. 59(2): 184-192.

SPENCER, M. D., CHURA, L. R., HOLT, R. J., SUCKLING, J., CALDER, A. J., BULLMORE, E. T. & BARON-COHEN, S. (2012a). Failure to deactivate the default mode network indicates a possible endophenotype of autism. *Molecular Autism*. 3(1): 1.

SPENCER, M. D., HOLT, R. J., CHURA, L. R., CALDER, A. J., SUCKLING, J., BULLMORE, E. T. & BARON-COHEN, S. (2012b). Atypical activation during the Embedded Figures Task as a functional magnetic resonance imaging endophenotype of autism. *Brain*. 135(11): 3469-3480.

SPENCER, M. D., MOORHEAD, T. W. J., LYMER, G. K. S., JOB, D. E., MUIR, W. J., HOARE, P., OWENS, D. G. C., LAWRIE, S. M. & JOHNSTONE, E. C. (2006). Structural correlates of intellectual impairment and autistic features in adolescents. *NeuroImage*. 33(4): 1136-1144.

STANFIELD, A. C., MCINTOSH, A. M., SPENCER, M. D., PHILIP, R., GAUR, S. & LAWRIE, S. M. (2008). Towards a neuroanatomy of autism: a systematic

review and meta-analysis of structural magnetic resonance imaging studies. *European Psychiatry*. 23(4): 289-299.

STARCKE, K., TUSCHEN-CAFFIER, B., MARKOWITSCH, H. J. & BRAND, M. (2010). Dissociation of decisions in ambiguous and risky situations in obsessive–compulsive disorder. *Psychiatry Research*. 175(1–2): 114-120.

STEELE, S. D., MINSHEW, N. J., LUNA, B. & SWEENEY, J. A. (2007). Spatial working memory deficits in autism. *Journal of Autism and Developmental Disorders*. 37(4): 605-612.

STEINBEIS, N., HAUSHOFER, J., FEHR, E. & SINGER, T. (2016). Development of Behavioral Control and Associated vmPFC–DLPFC Connectivity Explains Children's Increased Resistance to Temptation in Intertemporal Choice. *Cerebral Cortex*. 26(1): 32-42.

STEINGROEVER, H., WETZELS, R. & WAGENMAKERS, E.-J. (2014). Absolute performance of reinforcement-learning models for the Iowa Gambling Task. *Decision*. 1(3): 161.

STERN, E. R. & TAYLOR, S. F. (2014). Cognitive Neuroscience of Obsessive-Compulsive Disorder. *Psychiatric Clinics of North America*. 37(3): 337-352.

STIGLER, K. A., MCDONALD, B. C., ANAND, A., SAYKIN, A. J. & MCDOUGLE, C. J. (2011). Structural and functional magnetic resonance imaging of autism spectrum disorders. *Brain Research*. 1380146-161.

STROUP, D. F., BERLIN, J. A., MORTON, S. C. & ET AL. (2000). Meta-analysis of observational studies in epidemiology: A proposal for reporting. *Journal of the American Medical Association*. 283(15): 2008-2012.

STURM, H., FERNELL, E. & GILLBERG, C. (2004). Autism spectrum disorders in children with normal intellectual levels: associated impairments and subgroups. *Developmental Medicine & Child Neurology*. 46(7): 444-447.

STUSS, D. T. & ALEXANDER, M. P. (2007). Is there a dysexecutive syndrome? *Philosophical Transactions of the Royal Society B: Biological Sciences*. 362(1481): 901-915.

SUBIRÀ, M., ALONSO, P., SEGALÀS, C., REAL, E., LÓPEZ-SOLÀ, C., PUJOL, J., MARTÍNEZ-ZALACAÍN, I., HARRISON, B. J., MENCHÓN, J. M. & CARDONER, N. (2013). Brain Structural Alterations in Obsessive-Compulsive Disorder Patients with Autogenous and Reactive Obsessions. *PLoS ONE*. 8(9): e75273.

SWICK, D., ASHLEY, V. & TURKEN, U. (2011). Are the neural correlates of stopping and not going identical? Quantitative meta-analysis of two response inhibition tasks. *NeuroImage*. 56(3): 1655-1665.

SYMMS, M., JÄGER, H. R., SCHMIERER, K. & YOUSRY, T. A. (2004). A review of structural magnetic resonance neuroimaging. *Journal of Neurology, Neurosurgery & Psychiatry*. 75(9): 1235-1244.

SZESZKO, P., CHRISTIAN, C., MACMASTER, F., LENCZ, T., MIRZA, Y., TAORMINA, S., EASTER, P., ROSE, M., MICHALOPOULOU, G. & ROSENBERG, D. (2008). Gray matter structural alterations in psychotropic drug-naive pediatric obsessive-compulsive disorder: an optimized voxel-based morphometry study. *American Journal of Psychiatry*. 165(10): 1299-1307.

SZESZKO, P. R., MACMILLAN, S., MCMENIMAN, M., CHEN, S., BARIBAULT, K., LIM, K. O., IVEY, J., ROSE, M., BANERJEE, S. P. & BHANDARI, R. (2004). Brain structural abnormalities in psychotropic drug-naive pediatric patients with obsessive-compulsive disorder. *American Journal of Psychiatry*. 161(6): 1049-1056.

SZESZKO, P. R., ROBINSON, D., ALVIR, J. M. J., BILDER, R. M., LENCZ, T., ASHTARI, M., WU, H. & BOGERTS, B. (1999). Orbital frontal and amygdala

volume reductions in obsessive-compulsive disorder. *Archives of General Psychiatry*. 56(10): 913-919.

TAGER-FLUSBERG, H. (2007). Evaluating the Theory-of-Mind Hypothesis of Autism. *Current Directions in Psychological Science*. 16(6): 311-315.

TALAIRACH, J. & TOURNOUX, P. (1988). *Coplanar stereotaxic atlas of the human brain, a 3-dimensional proportional system: an approach to cerebral imaging*. Thieme: New York.

TAMURA, R., KITAMURA, H., ENDO, T., HASEGAWA, N. & SOMEYA, T. (2010). Reduced thalamic volume observed across different subgroups of autism spectrum disorders. *Psychiatry Research: Neuroimaging*. 184(3): 186-188.

TAN, L., FAN, Q., YOU, C., WANG, J., DONG, Z., WANG, X., CHEN, K., XIAO, Z. & JIANG, K. (2013). Structural changes in the gray matter of unmedicated patients with obsessive-compulsive disorder: a voxel-based morphometric study. *Neuroscience bulletin*. 29(5): 642-648.

TANAKA, S. C., DOYA, K., OKADA, G., UEDA, K., OKAMOTO, Y. & YAMAWAKI, S. (2004). Prediction of immediate and future rewards differentially recruits cortico-basal ganglia loops. *Nature neuroscience*. 7(8): 887-893.

TANG, W., HUANG, X., LI, B., JIANG, X., LI, F., XU, J., YANG, Y. & GONG, Q. (2015). Structural brain abnormalities correlate with clinical features in patients with drug-naïve OCD: A DARTEL-enhanced voxel-based morphometry study. *Behavioural Brain Research*. 29472-80.

TANG, W., LI, B., HUANG, X., JIANG, X., LI, F., WANG, L., CHEN, T., WANG, J., GONG, Q. & YANG, Y. (2013). Morphometric brain characterization of refractory obsessive–compulsive disorder: Diffeomorphic anatomic registration

using exponentiated Lie algebra. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 46126-131.

TAYLOR, S. (2011). Early versus late onset obsessive–compulsive disorder: Evidence for distinct subtypes. *Clinical Psychology Review*. 31(7): 1083-1100.

THAKKAR, K. N., POLLI, F. E., JOSEPH, R. M., TUCH, D. S., HADJIKHANI, N., BARTON, J. J. & MANOACH, D. S. (2008). Response monitoring, repetitive behaviour and anterior cingulate abnormalities in autism spectrum disorders (ASD). *Brain*. 131(9): 2464-2478.

THIRION, B., PINEL, P., MÉRIAUX, S., ROCHE, A., DEHAENE, S. & POLINE, J.-B. (2007). Analysis of a large fMRI cohort: Statistical and methodological issues for group analyses. *NeuroImage*. 35(1): 105-120.

THORPE, S., FIZE, D. & MARLOT, C. (1996). Speed of processing in the human visual system. *Nature*. 381(6582): 520-522.

TIEMEIER, H., LENROOT, R. K., GREENSTEIN, D. K., TRAN, L., PIERSON, R. & GIEDD, J. N. (2010). Cerebellum development during childhood and adolescence: a longitudinal morphometric MRI study. *NeuroImage*. 49(1): 63-70.

TOAL, F., DALY, E., PAGE, L., DEELEY, Q., HALLAHAN, B., BLOEMEN, O., CUTTER, W., BRAMMER, M., CURRAN, S. & ROBERTSON, D. (2010). Clinical and anatomical heterogeneity in autistic spectrum disorder: a structural MRI study. *Psychological Medicine*. 40(07): 1171-1181.

TOGA, A. W., THOMPSON, P. M. & SOWELL, E. R. (2006). Mapping brain maturation. *Focus*.

TOGAO, O., YOSHIURA, T., NAKAO, T., NABEYAMA, M., SANEMATSU, H., NAKAGAWA, A., NOGUCHI, T., HIWATASHI, A., YAMASHITA, K., NAGAO, E., KANBA, S. & HONDA, H. (2010). Regional gray and white

matter volume abnormalities in obsessive–compulsive disorder: A voxel-based morphometry study. *Psychiatry Research: Neuroimaging*. 184(1): 29-37.

TOLIN, D. F., WITT, S. T. & STEVENS, M. C. (2014). Hoarding disorder and obsessive–compulsive disorder show different patterns of neural activity during response inhibition. *Psychiatry Research: Neuroimaging*. 221(2): 142-148.

TRIVEDI, J., DHYANI, M., GOEL, D., SHARMA, S., SINGH, A., SINHA, P. & TANDON, R. (2008). Neurocognitive dysfunction in patients with obsessive compulsive disorder. *African Journal of Psychiatry*. 11(3): 204-209.

TURNER, R., HOWSEMAN, A., REES, G. E., JOSEPHS, O. & FRISTON, K. (1998). Functional magnetic resonance imaging of the human brain: data acquisition and analysis. *Experimental Brain Research*. 123(1-2): 5-12.

TYE, C., ASHERSON, P., ASHWOOD, K. L., AZADI, B., BOLTON, P. & MCLOUGHLIN, G. (2014). Attention and inhibition in children with ASD, ADHD and co-morbid ASD + ADHD: an event-related potential study. *Psychological Medicine*. 44(5): 1101-1116.

UDDIN, L. Q. & MENON, V. (2009). The anterior insula in autism: under-connected and under-examined. *Neuroscience & Biobehavioral Reviews*. 33(8): 1198-1203.

UDDIN, L. Q., MENON, V., YOUNG, C. B., RYALI, S., CHEN, T., KHOUZAM, A., MINSHEW, N. J. & HARDAN, A. Y. (2011). Multivariate searchlight classification of structural magnetic resonance imaging in children and adolescents with autism. *Biological Psychiatry*. 70(9): 833-841.

URSU, S., STENGER, V. A., SHEAR, M. K., JONES, M. R. & CARTER, C. S. (2003). Overactive Action Monitoring in Obsessive-Compulsive Disorder: Evidence From Functional Magnetic Resonance Imaging. *Psychological Science*. 14(4): 347-353.

VAIDYA, C. J., FOSS-FEIG, J., SHOOK, D., KAPLAN, L., KENWORTHY, L. & GAILLARD, W. D. (2011). Controlling attention to gaze and arrows in childhood: an fMRI study of typical development and Autism Spectrum Disorders. *Developmental science*. 14(4): 911-924.

VALENTE JR, A. A., MIGUEL, E. C., CASTRO, C. C., AMARO JR, E., DURAN, F. L. S., BUCHPIGUEL, C. A., CHITNIS, X., MCGUIRE, P. K. & BUSATTO, G. F. (2005). Regional Gray Matter Abnormalities in Obsessive-Compulsive Disorder: A Voxel-Based Morphometry Study. *Biological Psychiatry*. 58(6): 479-487.

VAN DEN HEUVEL, O. A., GROENEWEGEN, H. J., BARKHOF, F., LAZERON, R. H., VAN DYCK, R. & VELTMAN, D. J. (2003). Frontostriatal system in planning complexity: a parametric functional magnetic resonance version of Tower of London task. *NeuroImage*. 18(2): 367-374.

VAN DEN HEUVEL, O. A., MATAIX-COLS, D., ZWITSER, G., CATH, D. C., VAN DER WERF, Y. D., GROENEWEGEN, H. J., VAN BALKOM, A. J. L. M. & VELTMAN, D. J. (2011). Common limbic and frontal-striatal disturbances in patients with obsessive compulsive disorder, panic disorder and hypochondriasis. *Psychological Medicine*. 41(11): 2399-2410.

VAN DEN HEUVEL, O. A., REMIJNSE, P. L., MATAIX-COLS, D., VRENKEN, H., GROENEWEGEN, H. J., UYLINGS, H. B., VAN BALKOM, A. J. & VELTMAN, D. J. (2009). The major symptom dimensions of obsessive-compulsive disorder are mediated by partially distinct neural systems. *Brain*. 132(4): 853-868.

VAN DEN HEUVEL, O. A., VELTMAN, D. J., GROENEWEGEN, H. J. & ET AL. (2005a). Disorder-specific neuroanatomical correlates of attentional bias in

obsessive-compulsive disorder, panic disorder, and hypochondriasis. *Archives of General Psychiatry*. 62(8): 922-933.

VAN DEN HEUVEL, O. A., VELTMAN, D. J., GROENEWEGEN, H. J. & ET AL. (2005b). Frontal-striatal dysfunction during planning in obsessive-compulsive disorder. *Archives of General Psychiatry*. 62(3): 301-309.

VAN DER MEER, J. M. J., OERLEMANS, A. M., VAN STEIJN, D. J., LAPPENSCHAAR, M. G. A., DE SONNEVILLE, L. M. J., BUITELAAR, J. K. & ROMMELSE, N. N. J. (2012). Are Autism Spectrum Disorder and Attention-Deficit/Hyperactivity Disorder Different Manifestations of One Overarching Disorder? Cognitive and Symptom Evidence From a Clinical and Population-Based Sample. *Journal of the American Academy of Child & Adolescent Psychiatry*. 51(11): 1160-1172.e1163.

VAN DER WEE, N. J., RAMSEY, N. F., JANSMA, J. M., DENYS, D. A., VAN MEGEN, H. J., WESTENBERG, H. M. & KAHN, R. S. (2003). Spatial working memory deficits in obsessive compulsive disorder are associated with excessive engagement of the medial frontal cortex. *NeuroImage*. 20(4): 2271-2280.

VAN DER WEE, N. J., RAMSEY, N. F., VAN MEGEN, H. J., DENYS, D., WESTENBERG, H. G. & KAHN, R. S. (2007). Spatial working memory in obsessive–compulsive disorder improves with clinical response: a functional MRI study. *European Neuropsychopharmacology*. 17(1): 16-23.

VAN DUIJVENVOORDE, A. C. K., JANSEN, B. R. J., VISSER, I. & HUIZENGA, H. M. (2010). Affective and Cognitive Decision-Making in Adolescents. *Developmental Neuropsychology*. 35(5): 539-554.

VAN EYLEN, L., BOETS, B., STEYAERT, J., EVERS, K., WAGEMANS, J. & NOENS, I. (2011). Cognitive flexibility in autism spectrum disorder: Explaining the inconsistencies? *Research in Autism Spectrum Disorders*. 5(4): 1390-1401.

VAN VELZEN, L. S., VRIEND, C., DE WIT, S. J. & VAN DEN HEUVEL, O. A. (2014). Response inhibition and interference control in obsessive-compulsive spectrum disorders. *Frontiers in Human Neuroscience*. 8.

VAN WIJNGAARDEN-CREMERS, P. J. M., VAN EETEN, E., GROEN, W. B., VAN DEURZEN, P. A., OOSTERLING, I. J. & VAN DER GAAG, R. J. (2014). Gender and Age Differences in the Core Triad of Impairments in Autism Spectrum Disorders: A Systematic Review and Meta-analysis. *Journal of Autism and Developmental Disorders*. 44(3): 627-635.

VERHOEVEN, J. S., DE COCK, P., LAGAE, L. & SUNAERT, S. (2010). Neuroimaging of autism. *Neuroradiology*. 52(1): 3-14.

VERTE, S., GEURTS, H. M., ROEYERS, H., OOSTERLAAN, J. & SERGEANT, J. A. (2005). Executive functioning in children with autism and Tourette syndrome. *Development and psychopathology*. 17(02): 415-445.

VERTE, S., GEURTS, H. M., ROEYERS, H., OOSTERLAAN, J. & SERGEANT, J. A. (2006). Executive functioning in children with an autism spectrum disorder: Can we differentiate within the spectrum? *Journal of Autism and Developmental Disorders*. 36(3): 351-372.

VIA, E., RADUA, J., CARDONER, N., HAPPÉ, F. & MATAIX-COLS, D. (2011). Meta-analysis of gray matter abnormalities in autism spectrum disorder: Should asperger disorder be subsumed under a broader umbrella of autistic spectrum disorder? *Archives of General Psychiatry*. 68(4): 409-418.

VLOET, T., MARX, I., KAHRAMAN-LANZERATH, B., ZEPF, F., HERPERTZ-DAHLMANN, B. & KONRAD, K. (2010). Neurocognitive Performance in Children with ADHD and OCD. *Journal of abnormal child psychology*. 38(7): 961-969.

VOGAN, V. M., MORGAN, B. R., LEE, W., POWELL, T. L., SMITH, M. L. & TAYLOR, M. J. (2014). The neural correlates of visuo-spatial working memory in children with autism spectrum disorder: effects of cognitive load. *Journal of Neurodevelopmental Disorders*. 6(1): 1.

VOGT, B. A., FINCH, D. M. & OLSON, C. R. (1992). Functional Heterogeneity in Cingulate Cortex: The Anterior Executive and Posterior Evaluative Regions. *Cerebral Cortex*. 2(6): 435-443.

VOISIN, J., BIDET-CAULET, A., BERTRAND, O. & FONLUPT, P. (2006). Listening in Silence Activates Auditory Areas: A Functional Magnetic Resonance Imaging Study. *The Journal of Neuroscience*. 26(1): 273-278.

VÖLLM, B. A., TAYLOR, A. N., RICHARDSON, P., CORCORAN, R., STIRLING, J., MCKIE, S., DEAKIN, J. F. & ELLIOTT, R. (2006). Neuronal correlates of theory of mind and empathy: a functional magnetic resonance imaging study in a nonverbal task. *NeuroImage*. 29(1): 90-98.

VOON, V., DERBYSHIRE, K., RUCK, C., IRVINE, M. A., WORBE, Y., ENANDER, J., SCHREIBER, L. R. N., GILLAN, C., FINEBERG, N. A., SAHAKIAN, B. J., ROBBINS, T. W., HARRISON, N. A., WOOD, J., DAW, N. D., DAYAN, P., GRANT, J. E. & BULLMORE, E. T. (2015). Disorders of compulsivity: a common bias towards learning habits. *Mol Psychiatry*. 20(3): 345-352.

VOSSEL, S., GENG, J. J. & FINK, G. R. (2014). Dorsal and ventral attention systems distinct neural circuits but collaborative roles. *The Neuroscientist*. 20(2): 150-159.

VRIEND, C., DE WIT, S. J., REMIJNSE, P. L., VAN BALKOM, A. J. L. M., VELTMAN, D. J. & VAN DEN HEUVEL, O. A. (2013). Switch the itch: A naturalistic follow-up study on the neural correlates of cognitive flexibility in

obsessive-compulsive disorder. *Psychiatry Research: Neuroimaging*. 213(1): 31-38.

WAINWRIGHT-SHARP, J. A. & BRYSON, S. E. (1993). Visual orienting deficits in high-functioning people with autism. *Journal of Autism and Developmental Disorders*. 23(1): 1-13.

WAITER, G. D., WILLIAMS, J. H., MURRAY, A. D., GILCHRIST, A., PERRETT, D. I. & WHITEN, A. (2004). A voxel-based investigation of brain structure in male adolescents with autistic spectrum disorder. *NeuroImage*. 22(2): 619-625.

WAITER, G. D., WILLIAMS, J. H. G., MURRAY, A. D., GILCHRIST, A., PERRETT, D. I. & WHITEN, A. (2005). Structural white matter deficits in high-functioning individuals with autistic spectrum disorder: a voxel-based investigation. *NeuroImage*. 24(2): 455-461.

WANG, A. T., LEE, S. S., SIGMAN, M. & DAPRETTO, M. (2006). Neural basis of irony comprehension in children with autism: the role of prosody and context. *Brain*. 129(4): 932-943.

WANG, A. T., LEE, S. S., SIGMAN, M. & DAPRETTO, M. (2007). Reading Affect in the Face and Voice: Neural Correlates of Interpreting Communicative Intent in Children and Adolescents With Autism Spectrum Disorders. *Archives of General Psychiatry*. 64(6): 698-708.

WANG, S. S.-H., KLOTH, A. D. & BADURA, A. (2014). The cerebellum, sensitive periods, and autism. *Neuron*. 83(3): 518-532.

WATANABE, S. (2010). Asymptotic equivalence of Bayes cross validation and widely applicable information criterion in singular learning theory. *Journal of Machine Learning Research*. 11(Dec): 3571-3594.

WEBB, S. J., SPARKS, B.-F., FRIEDMAN, S. D., SHAW, D. W., GIEDD, J., DAWSON, G. & DAGER, S. R. (2009). Cerebellar vermal volumes and

behavioral correlates in children with autism spectrum disorder. *Psychiatry Research: Neuroimaging*. 172(1): 61-67.

WECHSLER, D. (1999). *Wechsler abbreviated scale of intelligence*. Psychological Corporation: San Antonio, TX.

WELSH, M. & PETERSON, E. (2014). Issues in the conceptualization and assessment of hot executive functions in childhood. *Journal of the International Neuropsychological Society*. 20(02): 152-156.

WESLEY, M. J. & BICKEL, W. K. (2014). Remember the Future II: Meta-analyses and Functional Overlap of Working Memory and Delay Discounting. *Biological Psychiatry*. 75(6): 435-448.

WESTWOOD, H., STAHL, D., MANDY, W. & TCHANTURIA, K. (2016). The set-shifting profiles of anorexia nervosa and autism spectrum disorder using the Wisconsin Card Sorting Test: a systematic review and meta-analysis. *Psychological Medicine*. FirstView1-19.

WHITE, S. W., OSWALD, D., OLLENDICK, T. & SCAHILL, L. (2009). Anxiety in children and adolescents with autism spectrum disorders. *Clinical Psychology Review*. 29(3): 216-229.

WHITESIDE, S. P., PORT, J. D. & ABRAMOWITZ, J. S. (2004). A meta–analysis of functional neuroimaging in obsessive–compulsive disorder. *Psychiatry Research: Neuroimaging*. 132(1): 69-79.

WHO (1992). *The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines*. Geneva: World Health Organization.

WIENER, M., TURKELTAUB, P. & COSLETT, H. B. (2010). The image of time: A voxel-wise meta-analysis. *NeuroImage*. 49(2): 1728-1740.

WIGGINS, L. D., ROBINS, D. L., ADAMSON, L. B., BAKEMAN, R. & HENRICH, C. C. (2012). Support for a Dimensional View of Autism Spectrum Disorders in Toddlers. *Journal of Autism and Developmental Disorders*. 42(2): 191-200.

WILLIAMS, D. L., GOLDSTEIN, G., CARPENTER, P. A. & MINSHEW, N. J. (2005). Verbal and spatial working memory in autism. *Journal of Autism and Developmental Disorders*. 35(6): 747-756.

WILLIAMS, D. L., GOLDSTEIN, G. & MINSHEW, N. J. (2006). The profile of memory function in children with autism. *Neuropsychology*. 20(1): 21-29.

WILSON, L. B., TREGELLAS, J. R., HAGERMAN, R. J., ROGERS, S. J. & ROJAS, D. C. (2009). A voxel-based morphometry comparison of regional gray matter between fragile X syndrome and autism. *Psychiatry Research: Neuroimaging*. 174(2): 138-145.

WING, L. & GOULD, J. (1979). Severe impairments of social interaction and associated abnormalities in children: Epidemiology and classification. *Journal of Autism and Developmental Disorders*. 9(1): 11-29.

WISE, T., RADUA, J., VIA, E., CARDONER, N., ABE, O., ADAMS, T. M., AMICO, F., CHENG, Y., COLE, J. H., DE AZEVEDO MARQUES PERICO, C., DICKSTEIN, D. P., FARROW, T. F. D., FRODL, T., WAGNER, G., GOTLIB, I. H., GRUBER, O., HAM, B. J., JOB, D. E., KEMPTON, M. J., KIM, M. J., KOOLSCHIJN, P. C. M. P., MALHI, G. S., MATAIX-COLS, D., MCINTOSH, A. M., NUGENT, A. C., O'BRIEN, J. T., PEZZOLI, S., PHILLIPS, M. L., SACHDEV, P. S., SALVADORE, G., SELVARAJ, S., STANFIELD, A. C., THOMAS, A. J., VAN TOL, M. J., VAN DER WEE, N. J. A., VELTMAN, D. J., YOUNG, A. H., FU, C. H., CLEARE, A. J. & ARNONE, D. (2016). Common and distinct patterns of grey-matter volume alteration in major

depression and bipolar disorder: evidence from voxel-based meta-analysis. *Mol Psychiatry*.

WITTMANN, M. (2009). The inner experience of time. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*. 364(1525): 1955-1967.

WITTMANN, M., LELAND, D. S. & PAULUS, M. P. (2007). Time and decision making: differential contribution of the posterior insular cortex and the striatum during a delay discounting task. *Experimental Brain Research*. 179(4): 643-653.

WITTMANN, M., SIMMONS, A. N., ARON, J. L. & PAULUS, M. P. (2010). Accumulation of neural activity in the posterior insula encodes the passage of time. *Neuropsychologia*. 48(10): 3110-3120.

WOLFF, J. J., HAZLETT, H. C., LIGHTBODY, A. A., REISS, A. L. & PIVEN, J. (2013). Repetitive and self-injurious behaviors: associations with caudate volume in autism and fragile X syndrome. *Journal of Neurodevelopmental Disorders*. 5(1): 12.

WOODS, C. M., VEVEA, J. L., CHAMBLESS, D. L. & BAYEN, U. J. (2002). Are Compulsive Checkers Impaired in Memory? A Meta- Analytic Review. *Clinical Psychology: Science and Practice*. 9(4): 353-366.

WOOLLEY, J., HEYMAN, I., BRAMMER, M., FRAMPTON, I., MCGUIRE, P. K. & RUBIA, K. (2008). Brain activation in paediatric obsessive–compulsive disorder during tasks of inhibitory control. *The British Journal of Psychiatry*. 192(1): 25-31.

WORTHY, D., PANG, B. & BYRNE, K. (2013a). Decomposing the roles of perseveration and expected value representation in models of the Iowa gambling task. *Frontiers in Psychology*. 4(640).

WORTHY, D. A., HAWTHORNE, M. J. & OTTO, A. R. (2013b). Heterogeneity of strategy use in the Iowa gambling task: A comparison of win-stay/lose-shift and

reinforcement learning models. *Psychonomic Bulletin & Review*. 20(2): 364-371.

XIAO, Z., QIU, T., KE, X., XIAO, X., XIAO, T., LIANG, F., ZOU, B., HUANG, H., FANG, H., CHU, K., ZHANG, J. & LIU, Y. (2014). Autism Spectrum Disorder as Early Neurodevelopmental Disorder: Evidence from the Brain Imaging Abnormalities in 2–3 Years Old Toddlers. *Journal of Autism and Developmental Disorders*. 44(7): 1633-1640.

XUE, G., LU, Z., LEVIN, I. P. & BECHARA, A. (2010). The impact of prior risk experiences on subsequent risky decision-making: the role of the insula. *NeuroImage*. 50(2): 709-716.

YANG, D. Y. J., BEAM, D., PELPHREY, K. A., ABDULLAHI, S. & JOU, R. J. (2016). Cortical morphological markers in children with autism: a structural magnetic resonance imaging study of thickness, area, volume, and gyrification. *Molecular Autism*. 7(1): 1-14.

YANG, X., MA, X., HUANG, B., SUN, G., ZHAO, L., LIN, D., DENG, W., LI, T. & MA, X. (2015). Gray matter volume abnormalities were associated with sustained attention in unmedicated major depression. *Comprehensive Psychiatry*. 6371-79.

YECHIAM, E., ARSHAVSKY, O., SHAMAY-TSOORY, S. G., YANIV, S. & AHARON, J. (2010). Adapted to explore: Reinforcement learning in Autistic Spectrum Conditions. *Brain and Cognition*. 72(2): 317-324.

YERYS, B. E., HEPBURN, S. L., PENNINGTON, B. F. & ROGERS, S. J. (2007). Executive function in preschoolers with autism: Evidence consistent with a secondary deficit. *Journal of Autism and Developmental Disorders*. 37(6): 1068-1079.

YERYS, B. E., WALLACE, G. L., HARRISON, B., CELANO, M. J., GIEDD, J. N. & KENWORTHY, L. E. (2009). Set-shifting in children with autism spectrum disorders: Reversal shifting deficits on the Intradimensional/Extradimensional Shift Test correlate with repetitive behaviors. *Autism*. 13(5): 523-538.

YERYS, B. E., WALLACE, G. L., JANKOWSKI, K. F., BOLLICH, A. & KENWORTHY, L. (2011). Impaired Consonant Trigrams Test (CTT) performance relates to everyday working memory difficulties in children with Autism Spectrum Disorders. *Child Neuropsychology*. 17(4): 391-399.

YEUNG, M. K., HAN, Y. M. Y., SZE, S. L. & CHAN, A. S. (2016). Abnormal frontal theta oscillations underlie the cognitive flexibility deficits in children with high-functioning autism spectrum disorders. *Neuropsychology*. 30(3): 281-295.

YEUNG, N., NYSTROM, L. E., ARONSON, J. A. & COHEN, J. D. (2006). Between-task competition and cognitive control in task switching. *The Journal of Neuroscience*. 26(5): 1429-1438.

YOO, S. Y., ROH, M.-S., CHOI, J.-S., KANG, D.-H., HA, T. H., LEE, J.-M., KIM, I. Y., KIM, S. I. & KWON, J. S. (2008). Voxel-based morphometry study of gray matter abnormalities in obsessive-compulsive disorder. *Journal of Korean medical science*. 23(1): 24-30.

YÜCEL, M., HARRISON, B. J., WOOD, S. J., FORNITO, A., WELLARD, R. M., PUJOL, J., CLARKE, K., PHILLIPS, M. L., KYRIOS, M. & VELAKOULIS, D. (2007). Functional and biochemical alterations of the medial frontal cortex in obsessive-compulsive disorder. *Archives of General Psychiatry*. 64(8): 946-955.

ZALLA, T., SAV, A.-M. & LEBOYER, M. (2009). Stimulus-reward association and reversal learning in individuals with asperger syndrome. *Research in Autism Spectrum Disorders*. 3(4): 913-923.

ZAREI, M., MATAIX-COLS, D., HEYMAN, I., HOUGH, M., DOHERTY, J., BURGE, L., WINMILL, L., NIJHAWAN, S., MATTHEWS, P. M. & JAMES, A. (2011). Changes in Gray Matter Volume and White Matter Microstructure in Adolescents with Obsessive-Compulsive Disorder. *Biological Psychiatry*. 70(11): 1083-1090.

ZELAZO, P. D., CRAIK, F. I. M. & BOOTH, L. (2004). Executive function across the life span. *Acta Psychologica*. 115(2–3): 167-183.

ZELAZO, P. D. & MÜLLER, U. (2007). Executive Function in Typical and Atypical Development. In *Blackwell Handbook of Childhood Cognitive Development* (ed. U. Goswami), pp. 445-469. Blackwell Publishers Ltd: Malden, MA.

ZHANG, L., DONG, Y., JI, Y., TAO, R., CHEN, X., YE, J., ZHANG, L., YU, F., ZHU, C. & WANG, K. (2015a). Trait-related decision making impairment in obsessive-compulsive disorder: evidence from decision making under ambiguity but not decision making under risk. *Scientific reports*. 5.

ZHANG, L., TANG, J., DONG, Y., JI, Y., TAO, R., LIANG, Z., CHEN, J., WU, Y. & WANG, K. (2015b). Similarities and Differences in Decision-Making Impairments between Autism Spectrum Disorder and Schizophrenia. *Frontiers in Behavioral Neuroscience*. 9(259).

ZIELINSKI, C. M., TAYLOR, M. A. & JUZWIN, K. R. (1991). Neuropsychological Deficits in Obsessive-Compulsive Disorder. *Cognitive and Behavioral Neurology*. 4(2): 110-126.

ZILBOVICIUS, M., GARREAU, B., SAMSON, Y., REMY, P., BARTHELEMY, C., SYROTA, A. & LELORD, G. (1995). Delayed maturation of the frontal cortex in childhood autism. *American Journal of Psychiatry*. 152(2): 248-252.

ZINKE, K., FRIES, E., ALTGASSEN, M., KIRSCHBAUM, C., DETTENBORN, L. & KLIEGEL, M. (2010). Visuospatial short-term memory explains deficits in

tower task planning in high-functioning children with autism spectrum disorder. *Child Neuropsychology*. 16(3): 229-241.